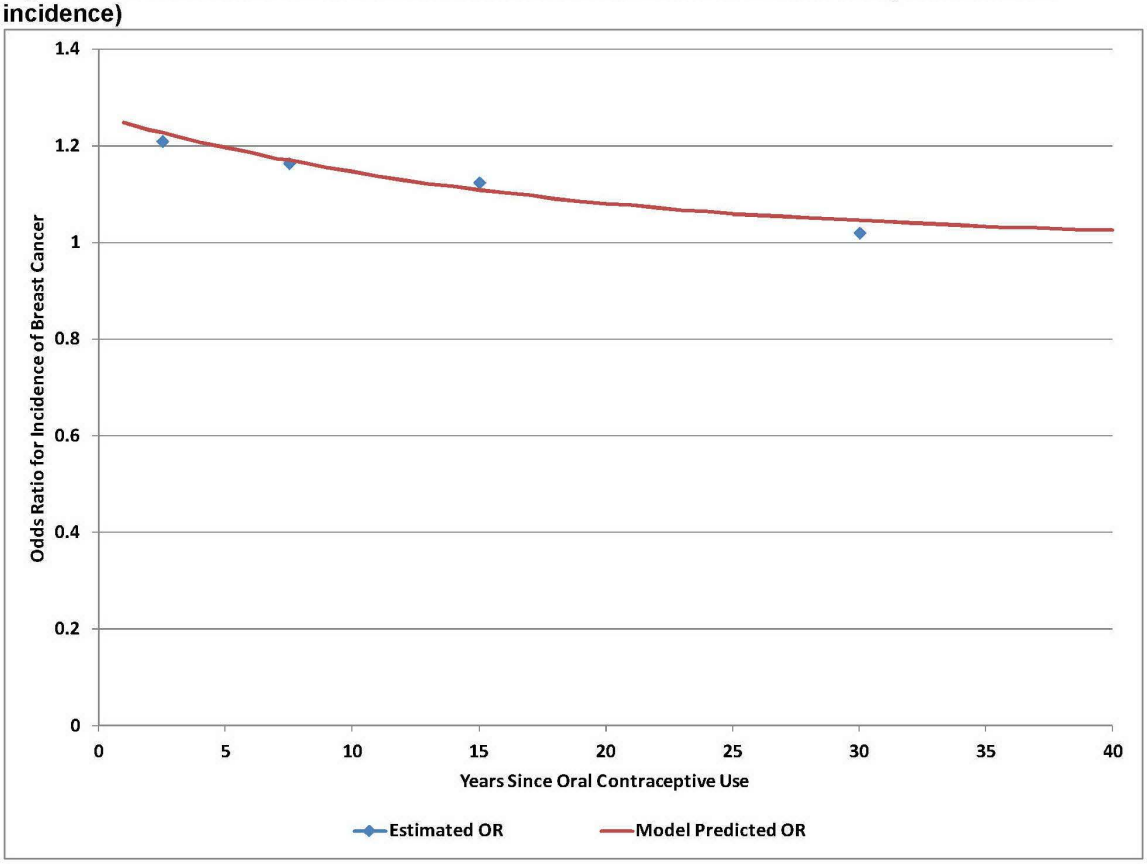
Figure 25. Estimated and model-fitted odds ratios for time since last OC use (breast cancer incidence)



OR = odds ratio

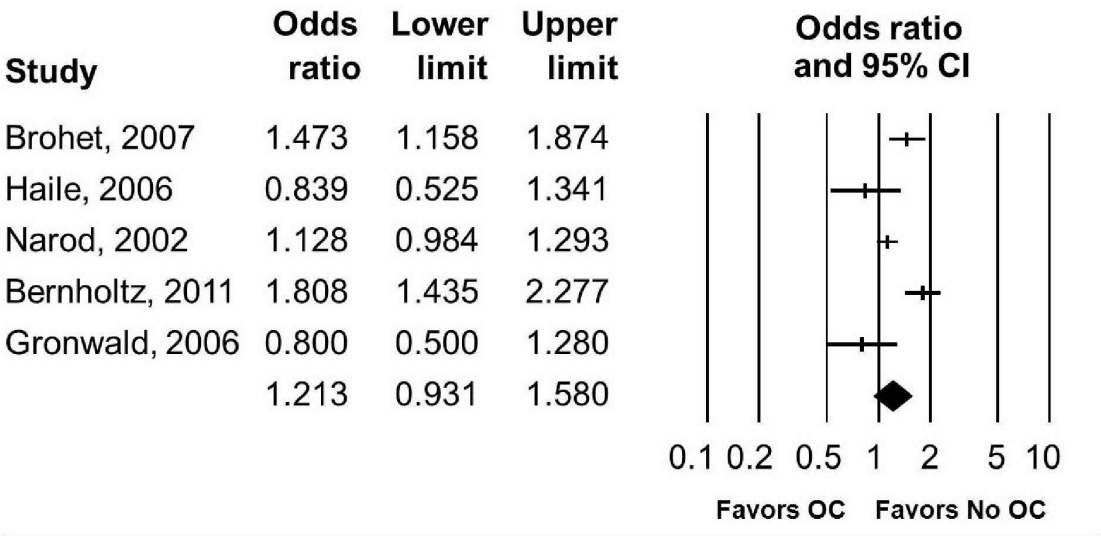
Special Populations

BRCA Mutation Carriers

We identified eight studies that were conducted with women who were BRCA1 or BRCA2 carriers.[94,190,198,199,208,212,220,225] Five BRCA1/2 carrier studies representing 4555 women across 4 studies and 65,180 person-years in 1 study assessed the risk of breast cancer as a function of OC use comparing BRCA carriers with each other and were included in a meta-analysis.[94,190,199,220,225] Three were case-control studies and two cohort studies; one was rated good quality and four fair quality. Two additional studies[198,208] examined the risk of breast cancer incidence in OC users among carriers of the BRCA mutation compared with control groups who were noncarriers, and one report[212] was conducted with BRCA carriers with either bilateral (cases) or unilateral (controls) cancers. Data from these three articles were not included in this meta-analysis.

Figure 26 shows pooled results indicating a slight, but not significant, increase in the risk of breast cancer among BRCA carriers who have ever used OCs, with an odds ratio of 1.21 (95% CI, 0.93 to 1.58). There was evidence of heterogeneity, with a Q-value of 20.005 for 4 degrees of freedom, $p<0.001$.

Figure 26. Forest plot for BRCA carriers compared with each other (breast cancer incidence)



CI = confidence interval; OC = oral contraceptive

Family History of Breast Cancer

We identified one case-control study[189] and two cohort studies[215,219] that assessed the risk of breast cancer among OC users with family histories of breast cancer, but these studies could not be pooled due to differences in study design and comparisons (Table 22). Of these studies, two were rated good quality and one fair quality. Overall, study results were mixed, possibly due to variation in how family history was defined across studies. One study[215] recruited first-degree, second-degree, and marry-in relatives of patients with breast cancer. Overall, this study found a significant increase in breast cancer for ever use (risk ratio [RR] 1.4; 95% CI, 1.0 to 2.0). This effect was greater among sisters and daughters (RR 3.3; CI, 1.6 to 6.7) but not among granddaughters and nieces of the affected family member (RR 1.2; CI, 0.8 to 2.0).

Another study[189] identified breast cancer families. A breast cancer family was defined as four cases of breast cancer (at any age), two breast cancer cases younger than 55 years of age, one case younger than 50 years, or a combination of breast cancer younger than 60 years of age and ovarian cancer (at any age) in a family. First-degree family members of affected women 40 to 60 years of age made up the pool of subjects for cases and controls. OC use was not associated with an increase in breast cancer (RR 0.90; 95% CI, 0.68 to 1.18). However, among BRCA1 mutation carriers, risk of breast cancer was associated with OC use, but the test was not significant (RR 2.00; CI, 0.36 to 10.9).

Another study[219] recruited women with either a first-degree or second-degree family member with breast cancer. OC use was associated with a reduction in risk of breast cancer among all women with breast cancer (hazard ratio [HR], 0.88; 95% CI, 0.73 to 1.07). However, among first-degree relatives, OC use did not reduce the risk of breast cancer (HR, 1.03; CI, 0.78 to 1.38). Among second-degree relatives, a protective effect for OC use was observed, but the comparison was not significant (HR, 0.74; CI, 0.54 to 1.00). This study highlights the heterogeneity of effects associated with multiple definitions of family history of breast cancer.

Table 22. Family history and association between OC use and breast cancer incidence

Study[a]	Study Details	Definition of Family History	OR	95% CI	Region	Study Quality
		Case-Control				
Heimdal, 2002[189]	Women aged 40–60 yr Cases: 380 Controls: 1043	First-degree family member	0.90	0.68 to 1.19	Norway	Fair
		Cohort				
Grabrick, 2000[215]	Family members of women aged 21–88 yr Exposed: 3156 Unexposed: 2994	First-degree, second-degree, or marry-in family member	1.4	1.0 to 2.0	U.S.	Good
Silvera, 2005[219]	Women aged 40–59 yr Exposed: 962 Unexposed: 745 *Women with first-degree relatives* Exposed: 433 Unexposed: 362 *Women with second-degree relatives* Exposed: 414 Unexposed: 284	First-degree or second-degree family member	0.88 1.03 0.74	0.73 to 1.07 0.78 to 1.38 0.54 to 1.00	Canada	Good

CI = confidence interval; OC = oral contraceptive; OR = odds ratio; U.S. = United States; yr = year/years
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

Breast Cancer in Younger Women

Three case-control studies[197,198,209] assessed the risk of breast cancer among younger women, defined as under 45 years of age at time of diagnosis (Table 18). Of these studies, one was good quality and two fair quality; all were conducted in Western countries. We were not able to quantitatively synthesize studies because one study was conducted in a special population[209] leaving only two studies. No clear pattern emerged from these studies. One study conducted among women with either ductal or lobular carcinomas[209] reported a significant increase in the odds of breast cancer among younger women who had ever used OCs (OR 1.21; 95% CI, 1.01 to 1.45). Two studies not conduced among special populations[197,198] did not find significant effects for ever use of OCs on risk of breast cancer (OR 1.65; 95% CI, 0.95 to 1.45[197] and OR 0.93; 95% CI, 0.69 to 1.24[198]).

Specific Types of Breast Cancers

Three case-control studies,[204,207,214], one cohort study,[223] and one pooled analysis[184] reported on associations between OCs and specific subtypes of breast cancer. Study characteristic and results of ever versus never use are presented in Table 23.

Three studies[184,214,223] assessed the risk of breast cancer subtypes defined by tumor hormone receptor protein expression status; i.e., estrogen receptor (ER), progesterone receptor, (PR) and human epidermal growth factor (HER2) protein expression or gene amplification. Differences in populations and methods precluded pooling studies. Overall, the two case-control studied did not demonstrate a statistically significant increase in the risk of these cancers associated with OC use. However, pooled analyses reported a significantly higher odds of triple-negative breast

cancer associated with OC use. Doole also reported that fewer years since last use and longer use of OCs significantly increased the risk of triple-negative breast cancers.

Two other studies[204,207] assessed the association of OC use and breast cancer subtypes not categorized by ER, PR, or HER2 status. One study[207] compared women in the United States with asynchronous bilateral breast cancer (cases) to women with unilateral breast cancer (controls) and found no significant association. One study[204] compared healthy community-based controls to women with cancer in situ 20 to 74 years of age. Similar to population studies of invasive breast cancer, this study found a small and significant increase in breast cancer in situ.

Table 23. Breast cancer subtype and association between OC use and breast cancer incidence

Study[a]	Study Details	Subtype of Breast Cancer	OR	95% CI	Region	Study Quality
Case-Control						
Nichols, 2007[204]	Women aged 20–74 yr in Collaborative Breast Cancer Study Cases: 1878 Controls: 8041 Recruitment period: 1997–2001	Breast cancer *in situ*	1.10	0.99 to 1.25	U.S.	Good
Figueiredo, 2008[207]	Women <55 yr in Women's Environment, and Radiation Epidemiology Study Cases: 708 asynchronous bilateral breast cancer Controls: 1399 unilateral breast cancer only Recruitment period: 1985–2000	Unilateral or bilateral breast cancer	0.88	0.67 to 1.16	U.S.	Fair
Ma, 2010[214]	White or African-American women aged 35–64 yr Cases: 335 triple-negative breast cancer, registries Controls: 2015, community Cases: 97 ER-/PR/HER2+ breast cancer, registries Controls: 2015, community Cases: 645 luminal A breast cancer, registries Controls: 2015, community Cases: 120 luminal B breast cancer, registries Controls: 2015, community Recruitment period: 2000–2003	Triple-negative, luminal A, luminal B, or ER-/PR-/HER2+ breast cancers	0.93 1.00 1.21 1.23	0.74 to 1.17 0.72 to 1.39 0.69 to 2.11 0.73 to 2.10	U.S.	Good

Table 23. Breast cancer subtype and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	Subtype of Breast Cancer	OR	95% CI	Region	Study Quality
		Cohort				
Rosenberg, 2010[223]	Women aged 21–69 yr in Black Women's Health Study Exposed: 445,824 person-years Unexposed: 128,768 person-years *ER+/PR+ receptor status* Cases: 284 *ER+/PR- receptor status* Cases: 80 *ER-/PR- receptor status* Cases: 46 Recruitment period: 1995	ER/PR receptor status breast cancers	IRR=1.11 IRR=0.97 IRR=1.65	0.86 to 1.42 0.61 to1.54 1.19 to 2.30	U.S.	Fair
		Pooled				
Dolle, 2009[184]	Women aged 21–45 yr in Seattle-Puget Sound Cases: 187 Controls: 1569 Recruitment periods: 1983–1990; 1990–1992	Triple-negative breast cancers	2.5	1.4 to 4.3	U.S.	Fair

CI = confidence interval; ER = estrogen receptor; HER = human epidermal growth factor receptor; IRR = incidence rate ratio; OC = oral contraceptive; OR = odds ratio; PR = progesterone receptor; U.S. = United States; yr=year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

OC Use and Breast Cancer Mortality

We identified six studies;[33,164-166,229-232] all six were cohort studies, and of these, three were rated good quality and three fair quality (Table 24). Three studies were based in the United States,[229,231,232] and the remaining studies were conducted in the United Kingdom.[33,165,230]

As with ovarian cancer mortality, the studies evaluated two different populations and questions. Three studies[33,165,232] evaluated population-level, cause-specific mortality from breast cancer (as well as other cancers, including ovarian cancer). The general question addressed was, "Are women who used OCs more likely to die from breast cancer than women who did not use OCs?" These studies did not find that OC use significantly increased risk.

Three other cohort studies[229-231] addressed the question, "Among women who develop breast cancer, are women who used OCs more or less likely to die from breast cancer within a certain time period than those who did not use OCs?" Again, no studies detected significant differences. Because studies did not report comparable statistics (e.g., hazard ratios, odds ratios), we did not perform meta-analyses.

Table 24. Study characteristics and association between OC use and breast cancer mortality

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality
Cohort						
Postdiagnosis Survival						
Trivers, 2007[231]	Women aged 20–54 yr with invasive breast cancer Exposed: 897 Unexposed: 367 Recruitment period: 1990–1992	1.00	0.77 to 1.29	Age, income	U.S.	Good
Wingo, 2007[229]	Women aged 20–54 yr in Cancer and Steroid Hormone Study Exposed: 2237 Unexposed: 1679 Recruitment period: 1980–1982	0.94	0.83 to 1.06	Age, race, menopausal status, BMI, education, income, time since last birth, use of HRT, radiation therapy	U.S.	Good
Barnett, 2008[230]	Women <55 yr in Studies of Epidemiology and Risk Factors in Cancer Heredity Exposed: 3069 Unexposed: 1357 Recruitment period: 1991–1996	0.93	0.78 to 1.1	Crude	UK	Fair
Population-Level Mortality						
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–1970	0.9	0.74 to 1.08	Age, parity, smoking, social class, HRT	UK	Fair
Vessey, 2010[165]	Oxford Family Planning Association Contraceptive Study (age NR) 602,700 person-years (total for exposed and unexposed) Recruitment period: 1968–1974	1	0.8 to 1.2	Age, parity, BMI, smoking, social class	UK	Fair

Table 24. Study characteristics and association between OC use and breast cancer mortality (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality
Cohort (continued)						
Population-Level Mortality (continued)						
Lu, 2011[232]	Women in the Women's Contraceptive and Reproductive Study (CARE) and the California Teachers Study (CTS) *CARE* Exposed: 3524 Unexposed: 1041	1.03	0.85 to 1.25	Age, race, BMI, age at menarche, smoking, study site, ER status, tumor stage, education, alcohol consumption, number of comorbidities, number of mammograms	U.S.	Good
	CTS Exposed: 2439 Unexposed: 1490	0.89	0.64 to 1.23	Age, race, BMI, age at menarche, smoking, CARE breast cancer cases		

BMI = body mass index; CI = confidence interval; HRT = hormone replacement therapy; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; yr=year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Odds ratios for meta-analysis of ever versus never OC use.

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Strength of Evidence for OC Use and Risk of Breast Cancer

As described in the Methods section, strength of evidence (SOE) assessments are based on consideration of four domains: risk of bias, consistency in direction of the effect, directness in measuring intended outcomes, and precision of effect. The degree of confidence that the observed effect of an intervention is unlikely to change is presented as SOE and can be insufficient, low, moderate, or high. Strength of evidence describes the adequacy of the current research, both quantity and quality, and whether the entire body of current research provides a consistent and precise estimate of effect. Interventions that have shown significant benefit in a small number of studies or have not yet been replicated using rigorous study designs will have insufficient or low strength of evidence, despite potentially offering clinically important benefits. Future research may find that the intervention is either effective or ineffective.

We rated the strength of evidence for the effect of ever use of OC on breast cancer incidence as moderate (Table 25). Future studies are not likely to impact the direction but may influence the magnitude of the effect toward a small but significant increase in the risk of breast cancer associated with having ever used OCs. Most studies were of good or fair quality and exhibited consistent findings. The overall confidence interval for the summary estimate demonstrates a high level of precision. However, all included studies were observational thus; some risk of bias due to limitations of the study designs may exist. The SOE for the duration of use on risk of breast cancer incidence is low; future studies may impact strength and direction of estimates. Results were inconsistent with high level of heterogeneity across studies. Furthermore, the quantitative synthesis of these studies was underpowered resulting in low precision and confidence in point estimates. As with the overall effect of OCs, there may be some risk of bias due to limitations of the observational study designs. The SOE for time since last use on the risk of breast cancer incidence was graded as low. It is likely that future studies may impact strength of estimates. There was significant heterogeneity of effects. Moreover, we were not able to assess the interaction of time since last use with other important time-dependent factors that could impact the overall estimate of effect (e.g., times since last use by age at first use).

The SOE for the association of OC use on breast cancers among women with a family history of breast cancer and in younger women at time of diagnosis was graded as insufficient. Differences in studies designs, such as how family history was defined, precluded quantitative synthesis. Moreover, there were only a handful of studies in each of these special populations and results were heterogeneous and exhibited inconsistent and imprecise findings. We graded the evidence as low among BRCA1/2 carriers. We were able to conduct a meta-analysis, but with only three studies; thus, precision and consistence were not optimal.

We graded the SOE for the risk of breast cancer mortality as moderate. The summary estimate included six large cohort studies that contributed a high level of precision. Results were consistent across studies. It is unlikely that future studies will influence the direction of this effect.

Table 25. Strength of evidence domains for the effect of OC use on breast cancer

Comparison	Number of Studies (Women and/or Person-years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Breast Cancer in Overall Population						
Ever vs. never use	23 (356,023 across 20 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Precise	Moderate 1.08 (1.00 to 1.17)
Duration of use	14 (291,407 across 12 studies and 2,898,072 person-years across 2 studies)	Medium	Inconsistent	Direct	Imprecise	Low No increase in risk for longer durations of use
Time since last use	11 (200,258)	High	Inconsistent	Direct	Imprecise	Low Reduced risk over time since last use 0–5 yr: 1.21 (1.04 to 1.41) 5–10 yr: 1.17 (0.98 to 1.38) 10–20 yr: 1.13 (0.97 to 1.31) >20 yr: 1.02 (0.88 to 1.18)
Incidence in BRCA1- or BRCA2-Positive Women						
Ever vs. never use	5 (4555 across 4 studies, and 65,180 person-years in 1 study)	Medium	Inconsistent	Direct	Imprecise	Low Trend toward slight increase in risk 1.21 (0.93 to 1.58)
Incidence in Women With Family History						
Ever vs. never use	3 (9280)	High	Inconsistent	Direct	Imprecise	Insufficient Not performed
Incidence in Young Women						
Ever vs. never use	3 (5716)	Medium	Inconsistent	Direct	Imprecise	Insufficient Not performed
Mortality From Breast Cancer						
Ever vs. never use	3 (54,606 across 2 studies and 602,700 person-years in 1 study)	Medium	Consistent	Direct	Imprecise	Low No significant increase in risk 0.94 (0.87 to 1.02)
Survival After Diagnosis of Breast Cancer						
Ever vs. never use	3 (9606)	Medium	Consistent	Direct	Imprecise	Low No significant increase in risk

BRCA = breast cancer genetic mutation; CI = confidence interval; SOE = strength of evidence; yr = year/years

OC Use and Cervical Cancer Incidence

We identified 12 studies that evaluated the association between OC use and the incidence of cervical cancer.[37,138,155,156,233-241] including two articles from an International Agency for Research on Cancer (IARC) study representing distinct populations.[240,241] Of these, nine were case-control studies, three cohort studies, and one pooled analysis; five studies were rated good quality, four fair quality, and four poor quality. Of the two articles from the IARC study, one was a pooled analysis and one a case-control design. Only two studies were conducted with U.S.-based populations and three were conducted among women selected for HPV+ infection status (Table 26).

Table 26. Study characteristics and association between OC use and cervical cancer incidence

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control							
Madeleine, 2001[233]	Women aged 18–70 yr in U.S. Surveillance, Epidemiology, and End Results (SEER) Cases: 150 cervical cancer, SEER registry Controls: 651, population Recruitment period: 1990–1996	2.7	1.2 to 5.8	Age, lifetime number of sex partners, interval since last screening pap smea	U.S.	Good	1
Santos, 2001[234]	Women recruited from hospitals in Lima (age NR) Cases: 186 invasive cervical cancer, hospitals Controls: 31, hospitals Recruitment period: 1996–1997	2.7	0.9 to 8.4	Age, screening history, age at first intercourse, ever pregnancy	Peru	Poor	2
Green, 2003[235]	White women aged 20–44 yr selected from 5 UK cancer registries Cases: 391 squamous cancer, registries Controls: 923, outpatients Cases: 180 adenocarcinoma, registries Controls: 923, outpatients Recruitment period: 1987–1989	1.37 1.56	0.97 to 1.94 1.01 to 2.42	Age, smoking, region, total number of sexual partners, age at first intercourse, duration of oral contraceptive use, number of negative screening results and education	UK	Good	1
Shapiro, 2003[236]	Women <60 yr at gynecological oncology clinics at tertiary care hospitals in Cape Town Cases: 524, invasive cervical cancer, hospitals Controls: 1541, hospitals Recruitment period: 1998–2001	0.8	0.7 to 1.1	Age, race, smoking, age at first sexual intercourse, lifetime sexual partners, number of pap smears, education, rural vs. urban	South Africa	Fair	1
Shields, 2004[237]	Patients aged 20–74 yr from hospitals in 5 U.S. cities Cases: 235 squamous cervical cancer, hospitals Controls: 209, community Recruitment period: 1982–1984	NR	NR	NA	U.S.	Poor	2

Table 26. Study characteristics and association between OC use and cervical cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Hammouda, 2005[241]	Women in Algeria Cases: 190, hospital Controls: 197, hospital Recruitment period: 1997–1999	NR	NR	NA	Algeria	Good	2
Nojomi, 2008[238]	Patients >30 yr from 1 of 7 general hospitals in Tehran Cases: 300, invasive cervical cancer, hospitals Controls: 319, hospitals Recruitment period: 2005–2006	0.9	0.6 to 1.2	NA (unadjusted)	Iran	Poor	1
Vanakankovit, 2008[239]	Patients aged 30–70 yr at a hospital in Bangkok Cases: 60 invasive cervical CA, hospital Controls: 180, hospital Recruitment period: 2006–2007	1.45	0.79 to 2.64	NA (unadjusted)	Thailand	Fair	1
Urban, 2012[155]	Black South African women aged 18–79 yr Cases: 241, hospital Controls: 156, hospital Recruitment period: 1995–2006	0.97	0.76 to 1.24	Age, parity, smoking, year of diagnosis, education, alcohol consumption, sexual partners, urban/rural residence, province of birth	South Africa	Good	1
Cohort							
Vessey, 2006[156]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study Exposed: 301,000 person-years Unexposed: 187,000 person-years Recruitment period: 1968–1974	4.2	1.8 to 12.0	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1

Table 26. Study characteristics and association between OC use and cervical cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Hannaford, 2007[37]	Royal College of General Practitioner's Oral Contraception Study Exposed: 744,000 person-years Unexposed: 339,000 person-years Mean age at study entry: 29 yr (SD 6.6) Recruitment period: 1968–1970	1.33	0.92 to 1.94	Age, parity, smoking, social status	UK	Fair	1
Rosenblatt, 2009[138]	Textile workers in Shanghai aged 30–64 yr Exposed: 352,695 person-years Unexposed: 2,057,377 person-years Recruitment period: 1989–1991	0.13	0.02 to 0.96	Age, parity	China	Poor	1
Pooled							
Moreno, 2002[240]	HPV-positive women in Europe, South America, and Asia Total sample Cases: 1,676 Controls: 255 Cases: 1,465 invasive cervical cancer Controls: 227 Cases: 211 cervical cancer *in situ* Controls: *28* Mean age of cases: 49 yr Recruitment period: NR	1.42 1.29 2.54	0.99 to2.04 0.88 to1.91 0.95 to6.78	Age, parity, study site, education, screening history, age at first intercourse, number of partners	Europe, South America, Asia	Fair	2

BMI = body mass index; CI = confidence interval; DMV = department of motor vehicles; ER = estrogen receptor; HRT = hormone replacement therapy; NA = not applicable; NR = not reported; NZ = New Zealand; OC = oral contraceptive; OR = odds ratio; PR = progesterone receptor; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Odds ratios for meta-analysis of ever versus never OC use.

[c]Meta-analysis code: 1 = Included in this meta-analysis; 2 = Excluded due to HPV-positive population

Ever Versus Never OC Use

HPV-Positive Populations

Persistent infection with one or more oncogenic HPV types is required for cervical carcinogenesis; thus, women with HPV represent the most relevant population to assess the risks associated of cervical cancer associated with OC use. Only three studies[234,237,240] assessed the association between OC use and cervical cancers among women positive for HPV (HPV+). Limited studies across comparisons precluded quantitative synthesis. We summarize each study below.

One fair-quality study[240] pooled data from eight case-control studies of HPV+ patients with cervical cancer. Ever use of OCs was associated with a statistically nonsignificant increase in the odds of invasive cervical cancer (OR 1.29; 95% CI, 0.88 to 1.91) and cervical cancer in situ (OR 2.54; CI, 0.95 to 6.78). However, duration of use was significantly associated with cancer incidence such that HPV+ women who used OCs for 5 to 9 years (OR 2.82; CI, 1.46 to 5.42) and 10 or more years (OR 4.03; CI, 2.09 to 8.02) experienced a significant increase in the risk of cervical cancers compared with never users. This estimate did not vary by time since first or last use. However, this trend was not observed for women who used OCs for less than 5 years.

Two case-control studies,[234,237] both rated poor quality, also assessed the risk of cervical cancer associated with OC use among HPV+ women. One study[234] recruited hospital based HPV+ cases and controls in Lima, Peru. Results of this study were included in the pooled analysis above, and thus, could not be combined again. Compared with HPV+ controls, HPV+ women who had ever used OCs were at elevated risk of cervical cancer compared with women who had never used OCs (OR 2.7; 95% CI, 0.90 to 8.4), but the contrast was not significant. This study did not compute any analysis by duration of use.

The other case-control study[237] assessed the association between OC use and cervical cancer among hospital-based HPV+ cases and HPV+ community controls in the United States. This study assessed the effect of duration of use on cervical cancer; the effect of ever use compared with never use was not calculated. Increasing the duration of OC use—categorized as less than 5 years, 5 to 10 years, and greater than 10 years—was associated with a decrease in cervical cancers. This trend was significant only in women with less than 5 years of use compared with never users (OR 0.6; 95% CI, 0.4 to 0.9).

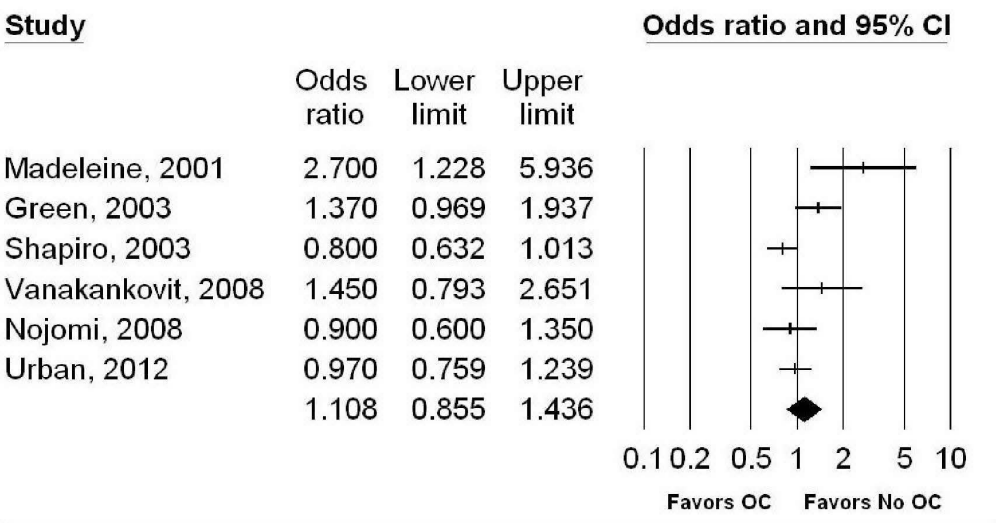
Populations Not Selected for HPV-Positive Status

Six case-control studies representing 5436 women[155,233,235,236,238,239] and three cohort studies[37,138,156] representing 3,981,072 person-years were included in this meta-analysis examining the effect of ever versus never OC use on cervical cancer incidence (Table 26). Of these studies, four were rated good quality, three fair quality, and two poor quality. We excluded datasets from this analysis for studies that were conducted among women who were HPV-positive or did not provide an estimate for ever versus never OC use.

Stratified by study type, pooled case-control studies (OR 1.11, 95% CI, 0.86 to 1.44) (Figure 27) and cohort studies (OR 1.20; CI, 0.33 to 4.34) (Figure 28) suggest an increased risk of cervical cancer among women who ever used OCs although these increases were not statistically significant. A meta-analysis of all nine included studies showed an increase in the odds of cervical cancer for women who had ever used OCs compared with women who never used OCs (OR 1.21; CI, 0.91 to 1.61), but the comparison again was not significant. There was a large

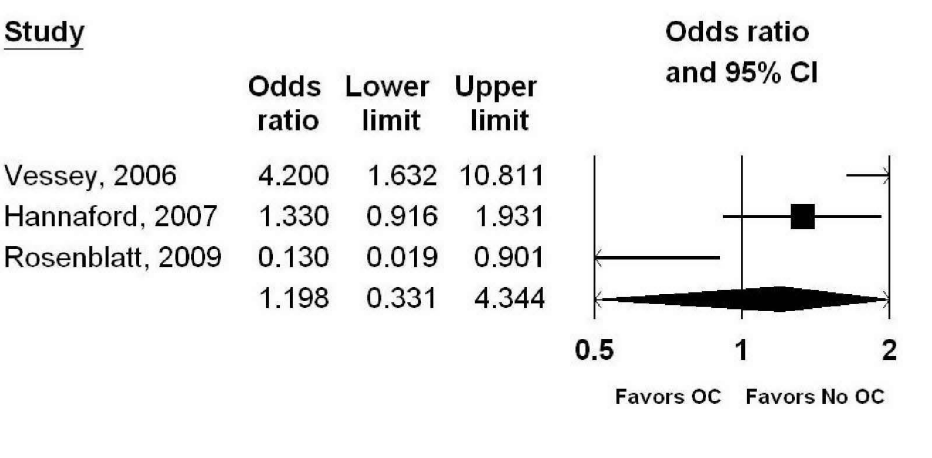
amount of heterogeneity, with a Q-value of 25.52 for 7 degrees of freedom, p<0.001, possibly due to HPV status differences among case-control studies, making the estimates unstable.

Figure 27. Forest plot for ever versus never OC use (case-control studies, cervical cancer incidence)



CI = confidence interval; OC = oral contraceptive

Figure 28. Forest plot for ever versus never OC use (cohort studies, cervical cancer incidence)



CI = confidence interval; OC = oral contraceptive

Sensitivity Analyses

We conducted additional analyses with only studies of good or fair quality. The magnitude of the effect was larger, but confidence intervals still included 1.0 (OR 2.17; 95% CI, 0.71 to 6.61). Only one study was conducted within the United States; results from this case-control study[233] show a similar quantitative increase in risk with ever use of OCs that was statistically significant (OR 2.7; CI, 1.2 to 5.8).

Duration of OC Use

Six studies[156,233,235,236,239,241] were included in this meta-analysis examining the effect of duration of OC use on cervical cancer incidence (Table 27). Of these, five were case-control studies and one was a cohort study; three were rated good quality and three fair quality. We excluded three studies from the meta-analysis[234,237,240] that presented duration data for a unique population (HPV+ women only).

Table 27. Data for outcomes on duration of OC use (cervical cancer incidence)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control				
Madeleine, 2001[233]		1–71 mo 72–143 mo ≥144 mo	2.1 3.4 5.5	1.0 to 4.8 1.5 to 8.0 2.1 to 14.6
Santos, 2001[234]		≤ 3 yr ≥ 4 yr	1.0 1.9	0.3 to 2.9 NR
Green, 2003[235]	Adenocarcinoma	1–5 yr 5–10 yr ≥ 10 yr	1.06 1.90 2.06	0.63 to 1.78 1.16 to 3.11 1.19 to 3.57
	Squamous cell cancer	1–5 yr 5–10 yr ≥ 10 yr	1.01 1.55 1.89	0.67 to 1.50 1.05 to 2.29 1.22 to 2.93
Shapiro, 2003[236]		≤ 1 yr 1–4 yr 5–9 yr ≥ 10 yr	0.8 0.8 0.5 1.7	0.6 to 1.1 0.6 to 1.2 0.3 to 1.0 0.9 to 3.1
Shields, 2004[237]		≤ 5 yr 5–10 yr ≥ 10 yr	0.6 0.7 0.5	0.4 to 0.9 0.4 to 1.3 0.3 to 1.0
Hammouda, 2005[241]		< 5 yr 5-9 yr ≥ 10 yr	0.6 0.5 0.8	0.3 to 1.2 0.3 to 1.1 0.4 to 1.6
Vanakankovit, 2008[239]		≤ 3 yr ≥ 3 yr	0.78 2.57	0.33 to 1.77 1.22 to 5.49
Cohort				
Vessey, 2006[156]		≤ 48 mo 49–96 mo ≥ 97 mo	2.9 3.3 6.1	0.9 to 9.9 1.2 to 10.4 2.5 to 17.0
Pooled				
Moreno, 2002[240]		≤ 1 yr 2–4 yr 5–9 yr > 10 yr	0.67 0.80 2.82 4.03	0.41 to1.08 0.51 to1.24 1.46 to5.42 2.09 to7.79

CI = confidence interval; mo = month/months; NR = not reported; OR = odds ratio; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

For the included studies we categorized duration of OC use into 2 intervals: (1) 1 to 60 months and (2) greater than 60 months. The results of this analysis, summarized in Table 28, show no time-dependent relationship as a function of duration. There was significant heterogeneity, with a t-value of 4.72 for 5 degrees of freedom, p=0.0033. The test was underpowered; there would have to be a 50-percent difference in risk of cervical cancer by time period in order to detect significant differences.

Table 28. Estimated odds ratios by duration of OC use (cervical cancer incidence)

Duration	Odds Ratio (95% Confidence Interval)	P-value
< 60 months	0.99 (0.58 to 1.70)	0.975
> 60 months	1.47 (0.91 to 2.38)	0.097

OC Use and Cervical Cancer Mortality

We identified two studies that evaluated the association between OC use and cervical cancer mortality (Table 29).[33,164-166] Both were cohort studies, rated fair quality, and were conducted in the United Kingdom. Vessey et al.[165] found an increased risk of cervical cancer mortality associated with OC use, with a very wide confidence interval, with a risk ratio of 7.3 (95% CI, 1.2 to 305). Hannaford et al.[33] found an increased risk of mortality among those exposed to OCs; however, these effects were not statistically significant, with a risk ratio of 1.52 (CI, 0.67 to 3.48). Both studies also assessed mortality as a function of duration of OC use; results showed a trend of increased risk of death with longer duration of use with a statistically significant increased risk of death for 8 or more years of use compared with never users.

Table 29. Study characteristics and association between OC use and cervical cancer mortality

Study	Study Details	Point Estimate (95% CI)[a]	Duration of Use	Point Estimate (95% CI)[b]	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort								
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–1970	1.34 (0.74 to 2.44)	< 4 yr 4–8 yr ≥ 8+ yr	1.08 (0.35 to 3.31) 1.60 (0.56 to 4.62) 2.97 (1.12 to 7.92)	Age, parity, smoking, social class	UK	Fair	1
Vessey, 2010[165]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study 602,700 person-yr (total for exposed and unexposed) Recruitment period: 1968–1974	7.3 (1.2 to 305.0)	< 48 mo 49–96 mo ≥ 97 mo	3.8 (0.30 to 1.98) 7.7 (0.9 to 3.56) 10.2 (1.40, to 4.47)	Age, parity, BMI, smoking, social class	UK	Fair	1

BMI = body mass index; CI = confidence interval; DMV = department of motor vehicles; ER = estrogen receptor; HRT = hormone replacement therapy; IRR = incidence rate ratio; mo = month; NR = not reported; OC = oral contraceptive; SD = standard deviation; UK = United Kingdom; yr = year/years

[a]Point estimate for meta-analysis of ever versus never OC use.

[b]Point estimate for meta-analysis of duration of OC use.

[c]Meta-analysis code: 1 = Met inclusion criteria for possible meta-analysis.

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Strength of Evidence for OC Use and Risk of Cervical Cancer

We graded the SOE for the association of ever use of OC on the risk of cervical cancer among HPV+ women as insufficient (Table 30). We identified only three studies and most were of poor quality. Studies did not control for factors that may influence risk such as age at first use by duration or age at sexual debut, which is likely highly correlated with age at first use. Moreover, results were inconsistent; sensitivity analysis yielded qualitatively different estimates of effects; and confidence intervals were wide. Future studies will likely influence magnitude and, possibly, direction of effect.

The SOE for the risk of cervical cancer mortality associated with the use of OCs was graded as low. Though results were consistent and suggest increased risk of death associated with prolonged use, we identified only two studies. Results lacked precision; studies reported very wide confidence intervals. Risk of bias was graded as high; studies did not account for HPV status and both were rated only fair quality. Future research will likely moderate the magnitude and direction of effects.

Table 30. Strength of evidence domains for the effect of OC use on cervical cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Cervical Cancer in HPV-Positive Population						
Ever vs. never use	3 (2592)	High	Inconsistent	Direct	Imprecise	Insufficient Unable to draw summary conclusion
Mortality From Cervical Cancer						
Ever vs. never use	2 (46,112 women in 1 study and 602,700 person-years in 1 study)	High	Consistent	Direct	Imprecise	Low Increased risk with ever use and longer duration of use

CI = confidence interval; HPV = human papillomaviruses; SOE = strength of evidence

OC Use and Colorectal Cancer Incidence

We identified 11 studies that evaluated the association between OC use and the incidence of colorectal cancer.[37,88,99,156,242-249] Of these, 3 were case-control studies, 7 cohort studies, and 1 pooled analysis; 4 studies were rated good quality, 6 fair quality and 1 poor quality (Table 31). Nine studies were conducted in Western countries and two in China.

Table 31. Study characteristics and association between OC use and colorectal cancer incidence

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control							
Levi, 2003[242]	Women aged 28–74 yr in Canton of Vaud Cases: 131 colorectal cancer, hospital Controls: 373, hospital Recruitment period: 1992–2001	0.83	0.4 to 1.7	Age, parity, family history, fiber intake, physical activity	Switzerland	Poor	1
Campbell, 2007[243]	Women aged 20–74 yr in Ontario, Newfoundland, Labrador Cases: 1404 colorectal cancer, registry Controls: 1203, property records Recruitment period: 2003–2006	0.77	0.65 to 0.91	Age, province of residence, education, ever use postmenopausal hormones, colorectal cancer screening endoscopy, physical activity, BMI, menopausal status	Canada	Fair	1
Long, 2010[244]	Women aged 40–80 yr in North Carolina Colon Cancer Study-II Cases: 443 distal large bowel cancer, registry Controls: 405, community Recruitment period: 2001–2006	0.95	0.67 to 1.34	Age, race, BMI, family history, smoking, family history of colorectal cancer, education, HRT use, physical activity	U.S.	Good	1
Cohort							
Rosenblatt, 2004[249]	Textile workers in Shanghai aged 30–64 yr Exposed: 352,851 person-years Unexposed: 1,045,388 person-years Recruitment period: 1989–1991	1.09	0.86 to 1.37	Age, parity	China	Fair	1
Vessey, 2006[156]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study Exposed: 301,000 person-years Unexposed: 187,000 person-years Recruitment period: 1968–1974	0.8	0.6 to 1.2	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1

Table 31. Study characteristics and association between OC use and colorectal cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Hannaford, 2007[37]	Royal College of General Practitioner's Oral Contraception study Exposed: 744,000 person-years Unexposed: 339,000 person-years Mean age at entry: 29 (SD6.6) Recruitment period: 1968–NR	0.72	0.58 to 0.90	Age, parity, smoking, social status	UK	Fair	1
Lin, 2007[246]	Women ≥45 yr in Women's Health Study Exposed: 27,440 Unexposed: 12,060 Recruitment period: 1992–NR	0.67	0.50 to 0.89	Age, BMI, family history, smoking, randomized treatment assignment, family history of colorectal cancer, previous history of benign colorectal polyps, physical activity, red meat intake, alcohol consumption, baseline aspirin use, multivitamin use, baseline postmenopausal hormone use	U.S.	Good	1
Kabat, 2008[245]	Women aged 40–59 yr in Canadian National Breast Screening Study Exposed: 1142 Unexposed: 88,655 Recruitment period: 1980–1985	0.83	0.73 to 0.94	Age, parity, smoking, social status, ever use of HRT	Canada	Fair	1
Dorjgochoo, 2009[88]	Women aged 40–70 yr in Shanghai Women's Health Study Exposed: 12,957 Unexposed: 15,557 Recruitment period: 1997–2000	1.24	0.87 to 1.78	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods	China	Fair	1

Table 31. Study characteristics and association between OC use and colorectal cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Tsilidis, 2010[247]	Women aged 35–70 yr in European Prospective Investigation into Cancer and Nutrition Exposed: 196,862 Unexposed: 139,399 Recruitment period: 1990s	0.92	0.83 to 1.02	Age, BMI, smoking, diabetes mellitus, physical activity, alcohol use	10 European countries	Good	1
Pooled							
Nichols, 2005[248]	Women in Wisconsin aged 20–74 yr Cases: 1488 colorectal cancer, registry Controls: 4297, community Recruitment periods: 1988–1991; 1997–2001	0.89	0.75 to 1.06	BMI, family history, smoking, conditional on age and study of enrollment; adjusted for family history of colorectal cancer, education, screening, hormone replacement therapy, age at first birth	U.S.	Fair	1

BMI = body mass index; CI = confidence interval; DMV = department of motor vehicles; ER = estrogen receptor; HRT = hormone replacement therapy; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; PR = progesterone receptor; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Odds ratio for meta-analysis of ever versus never OC use.

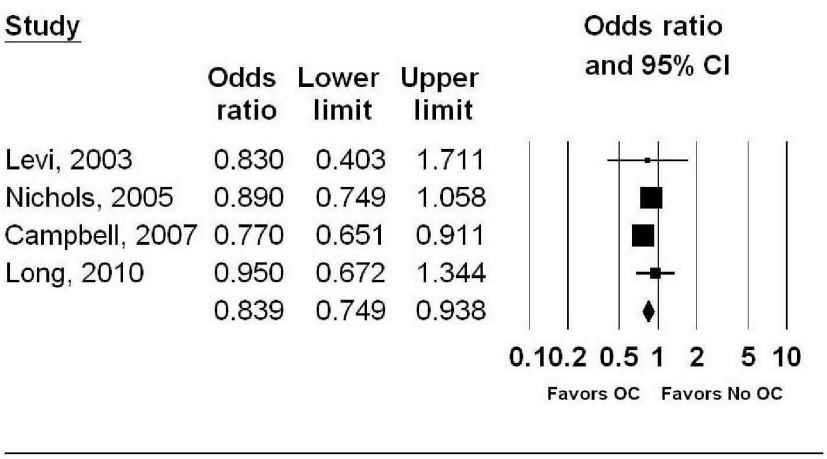
[c]Meta-analysis code: 1 = included in this meta-analysis.

Ever Versus Never OC Use

Three case-control studies,[242-244] one pooled analysis,[248] and seven cohort studies[37,88,156,245-247,249] representing 503,816 women across 8 studies and 2,969,189 person-years across 3 studies were included in this meta-analysis examining the effect of ever versus never OC use on colorectal cancer incidence (Table 31). Of these studies, four were rated good quality, six fair quality and one poor quality.

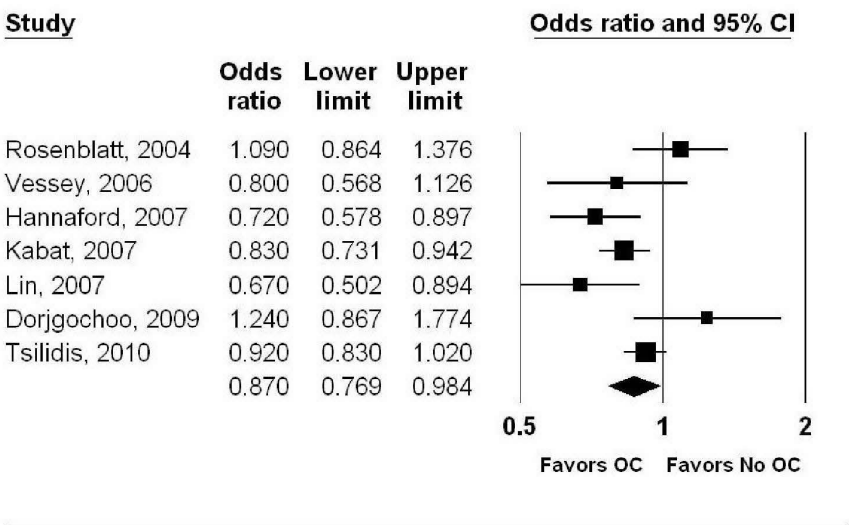
Stratified by study type, both case-control studies (OR 0.84; 95% CI, 0.75 to 0.94) (Figure 29) and cohort studies (OR 0.87; CI, 0.77 to 0.98) (Figure 30) demonstrated a decrease in the risk of colorectal cancers among women who ever used OCs. The odds ratios for the two types of studies were similar; a test of differences was not significant (p=0.791). In a meta-analysis including the 11 studies of all designs, the odds of colorectal cancer were significantly decreased for women who had ever used OCs compared with women who never used OCs (OR 0.86; CI, 0.79 to 0.95; Q value of 17.17, p<0.046).

Figure 29. Forest plot for ever versus never OC use (case-control and pooled studies, colorectal cancer incidence)



CI = confidence interval; OC = oral contraceptive

Figure 30. Forest plot for ever versus never OC use (cohort studies, colorectal cancer incidence)



CI = confidence interval; OC = oral contraceptive

Sensitivity Analyses

We conducted additional analyses including only studies of good or fair quality. Results were similar to those including all studies (OR 0.86; 95% CI, 0.79 to 0.94). We also conducted sensitivity analyses of studies that only included patients from the United States; results were similar to those containing all studies but the confidence interval eclipsed 1 (OR 0.83; CI, 0.69 to 1.01).

Duration of OC Use

Ten studies[37,88,156,242-246,248,249] were included in this meta-analysis examining the effect of duration of OC use on colorectal cancer incidence (Table 32). Of these, 3 were case-control studies, 6 cohort studies, and 1 pooled analysis; three were rated good quality, six fair quality and one poor quality. We excluded one study from the meta-analysis[247] that used less than 1 year of use as the reference group.

Table 32. Data for outcomes on duration of OC use (colorectal cancer incidence)

Study[a]	Duration	OR	95% CI
Case-Control			
Levi, 2003[242]	< 5 yr > 5 yr	0.74 0.87	0.2 to 2.4 0.4 to 2.0
Campbell, 2007[243]	1–4 yr ≥ 5 yr	0.77 0.77	0.62 to 0.97 0.62 to 0.95
Long, 2010[244]	0–2 yr >2 to < 5 yr 5 to < 10 yr > 10 yr	0.63 1.11 1.18 1.32	0.38 to 1.03 0.61 to 2.00 0.70 to 2.00 0.79 to 2.21
Cohort			
Rosenblatt, 2004[249]	< 6 mo 7–24 mo 25–36 mo ≥ 37 mo	0.97 0.96 1.13 1.56	0.64 to 1.47 0.67 to 1.38 0.65 to 1.97 1.01 to 2.40
Vessey, 2006[156]	< 48 mo 49–96 mo ≥ 97 mo	1.1 0.8 0.8	0.6 to 1.7 0.4 to 1.2 0.5 to 1.2
Hannaford, 2007[37]	<48 mo 49–96 mo ≥ 96 mo	0.82 0.72 0.95	0.51 to 1.31 0.43 to 1.21 0.59 to 1.54
Lin, 2007[246]	< 6 mo 6–35 mo 36–59 mo ≥ 60 mo	0.65 0.61 0.79 0.68	0.39 to 1.08 0.40 to 0.94 0.51 to 1.23 0.47 to 0.99
Kabat, 2008[245]	1–11 mo 12–25 mo 26–71 mo ≥ 72 mo	0.86 0.89 0.75 0.84	0.70 to 1.06 0.73 to 1.09 0.63 to 0.90 0.69 to 1.03
Dorjgochoo, 2009[88]	< 2 yr ≥ 2 yr	1.39 1.14	0.86 to 2.23 0.73 to 1.78
Tsilidis, 2010[247]	2–4 yr 5–9 yr ≥ 10 yr	0.99 0.93 1.09	0.80 to1.23 0.74 to 1.17 0.89 to 1.35
Pooled			
Nichols, 2005[248]	1–23 mo 24–53 mo 54–107 mo ≥ 108 mo	0.88 0.96 0.90 0.84	0.67 to 1.15 0.74 to 1.25 0.69 to 1.17 0.64 to 1.09

CI = confidence interval; mo = month/months; OR = odds ratio; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

For the included studies, we categorized duration of use into 2 intervals: (1) 1 to 60 months and (2) greater than 60 months. The results of this analysis, summarized in Table 33, show no time-dependent relationship as a function of duration. There was no significant heterogeneity, with a t-value of 1.52 for 9 degrees of freedom, p=0.164. As with most of the other analyses of duration of exposure, the test was underpowered; there would have to be a 20-percent difference in risk of colorectal cancer by time period in order to detect significant differences.

Table 33. Estimated odds ratios by duration of OC use (colorectal cancer incidence)

Duration	Odds Ratio (95% Confidence Interval)	P-value
< 60 months	0.88 (0.77 to 1.01)	0.063
> 60 months	0.88 (0.76 to 1.01)	0.061

OC Use and Colorectal Cancer Mortality

We identified two studies that evaluated the association between OC use and colorectal cancer mortality (Table 34).[33,164-166] Both were cohort studies, rated fair quality, and were conducted in the United Kingdom. Results were mixed. One study[33] found a decrease in the risk of mortality among those exposed to OCs; however, these effects were not statistically significant. The other study[165] showed an increase in colorectal cancer mortality associated with having ever used OCs. Both studies also assessed mortality as a function of duration of OC use; results showed no clear trend of a greater protective effect associated with longer duration of use.

Table 34. Study characteristics and association between OC use and colorectal cancer mortality

Study	Study Details	Point Estimate (95% CI)[a]	Duration of Use	Point Estimate (95% CI)[b]	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort								
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–NR	0.62 (0.46 to 0.83)	< 4 yr 4–8 yr ≥ 8+ yr	1.02 (0.52 to 2.0) 0.65 (0.30 to 1.43) 0.45 (0.16, 1.28)	Age, parity, smoking, social class	UK	Fair	1
Vessey, 2010[165]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study 602,700 person-yr (total for exposed and unexposed) Recruitment period: 1968–1974	1.2 (0.8 to 2.0)	< 48 mo 49–96 mo ≥ 97 mo	1.2 (0.6 to 2.4) 1.4 (0.7 to 2.5) 1.1 (0.6 to 2.0	Age, parity, BMI, smoking, social class	UK	Fair	1

BMI = body mass index; CI = confidence interval; mo = month/months; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; yr = year/years
[a]Point estimate for meta-analysis of ever versus never OC use.
[b]Point estimate for meta-analysis of duration of OC use.
[c]Meta-analysis code: 1=Met inclusion criteria for possible meta-analysis

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Strength of Evidence for OC Use and Risk of Colorectal Cancer

We graded the SOE for the association of OC use and incidence of colorectal cancer as moderate (Table 35). We were able to include all 11 studies in meta-analysis, results were consistent across studies and sensitivity analyses, and summary estimate demonstrated high precision with at tight confidence interval. Future studies will likely not impact direction of effect but may slightly influence magnitude of the effect. The SOE for duration was graded as insufficient. The test was underpowered and we found significant heterogeneity. Future studies will likely influence magnitude of effect across duration categories.

We also graded the SOE at insufficient for the risk of death associated with ever use of OCs. We identified only two fair-quality studies with inconsistent effects for ever use and duration of use. It is likely that future studies will impact direction and magnitude of effects.

Table 35. Strength of evidence domains for the effect of OC use on colorectal cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Colorectal Cancer in Overall Population						
Ever vs. never use	11 (503,816 across 8 studies and 2,969,189 person-years across 3 studies)	Medium	Consistent	Direct	Precise	Moderate 0.86 (0.79 to 0.95)
Duration of use	10 (167,555 across 7 studies and 2,969,189 person-years across 3 studies)	Medium	Consistent	Direct	Imprecise	Low No increase in protective effect with prolonged use
Mortality From Colorectal Cancer						
Ever vs. never use	2 (46,112 in 1 study and 602,700 person-years in a second study)	Medium	Inconsistent	Direct	Imprecise	Insufficient Mixed results for risk of death with ever use and no trend toward increased protective effect with longer duration of use

CI = confidence interval; SOE = strength of evidence

OC Use and Endometrial Cancer Incidence

We identified nine studies that evaluated the association between OC use and the incidence of endometrial cancer.[37,138,155,156,250-254] Of these, four were case-control studies and five cohort studies; six were rated good quality, two fair quality, and one poor quality. Only two studies were conducted in the United States (Table 36).

Table 36. Study characteristics and association between OC use and endometrial cancer incidence

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control							
Parslov, 2000[250]	Danish women aged 25–49 yr Cases: 237 endometrial cancer, hospital Controls: 538, Central Person Register Recruitment period: 1987–1994	NR	NR	NA	Denmark	Good	2
Maxwell, 2006[251]	Women aged 20–54 yr in Cancer and Steroid Hormone Study Cases: 434 endometrial cancer, SEER registry Controls: 2557, population *High progestin/high estrogen* *High progestin/low estrogen* *Low progestin/high estrogen* *Low progestin/Low estrogen* Recruitment period: 1980–1982	0.21 0.00 0.39 0.40	0.10 to 0.43 0.00 to 5.59 0.25 to 0.60 0.21 to 0.76	NA	U.S.	Good	1
Tao, 2006[254]	Women aged 30–69 yr in Shanghai Endometrial Cancer Study Cases: 1204 endometrial cancer, registry Controls: 1212 no history of hysterectomy, resident registry Recruitment period: 1997–2003	0.75	0.60 to 0.93	Age, parity, menopausal status, BMI, family history, age at menarche, education, yr of menstruation, family history of breast, endometrial, and colon cancers, age at last live birth, physical activity, exogenous hormone use	China	Good	1

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Table 36. Study characteristics and association between OC use and endometrial cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Urban, 2012[155]	Black South African women aged 18–79 yr Cases: 17, hospital Controls: 156, hospital Recruitment period: 1995–2006	1.01	0.55 to 1.85	Age, parity, smoking, year of diagnosis, education, alcohol consumption, sexual partners, urban/rural residence, province of birth	South Africa	Good	1
Cohort							
Vessey, 2006[156]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study Exposed: 301,000 person-years Unexposed: 187,000 person-years Recruitment period: 1968–1974	0.3	0.2 to 0.6	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1
Hannaford, 2007[37]	Royal College of General Practitioner's Oral Contraception Study Exposed: 744,000 person-years Unexposed: 339,000 person-years Mean age at study entry: 29 (SD 6.6) Recruitment period: 1968–NR	0.58	0.42 to 0.79	Age, parity, smoking, social status	UK	Fair	1
Setiawan, 2007[253]	Women aged 45–75 yr in Multiethnic Cohort Study Hawaii and Los Angeles 46,933 (total population of exposed and unexposed, postmenopausal women) Recruitment period: 1993–1996	NR	NR	NA	U.S.	Good	2
Rosenblatt, 2009[138]	Textile workers in Shanghai aged 30–64 yr Exposed: 352,695 person-years Unexposed: 2,057,377 person-years Recruitment period: 1989–1991	0.68	0.45 to 1.04	Age, parity, tubal ligation	China	Poor	1

Table 36. Study characteristics and association between OC use and endometrial cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Dossus, 2010[252]	European Prospective Investigation into Cancer and Nutrition Exposed: 1017 Unexposed: 301,601 1017 Cases, 301601 Cases Mean age of cases at entry: 56.2 Recruitment period: 1992–NR	0.65	0.56 to 0.75	BMI, smoking, physical activity, alcohol, diabetes, education	10 European countries	Fair	1

BMI = body mass index; CI = confidence interval; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Odds ratio for meta-analysis of ever versus never OC use.

[c]Meta-analysis code: 1 = Included in this meta-analysis; 2 = Excluded due to ever versus never OR not reported.

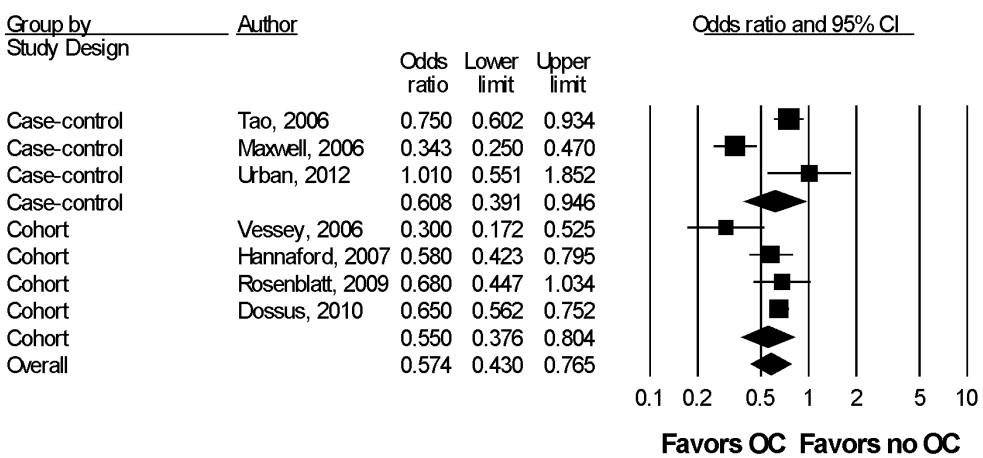
00803422

Ever Versus Never OC Use

Three case-control[155,251,254] and 4 cohort studies[37,138,156,252] representing 308,198 women (within 4 studies) and an additional 3,981,072 person-years (within the other 3 studies) were included in this meta-analysis examining the effect of ever versus never OC use on endometrial cancer incidence (Table 36). Of these studies, four were rated good quality, two fair quality, and 1 poor quality. We excluded two studies from the meta-analysis that did not report point estimates for ever versus never OC use.

Figure 31 indicates a protective effect for endometrial cancer associated with having ever used OCs (OR 0.57; 95% CI, 0.43 to 0.76). The test of heterogeneity was significant, with a Q-value of 26.11 for 6 degrees of freedom, p<0.001. However, test for a difference between the cohort and case-control studies was not significant, with a Q-value of 0.113 for 1 degree of freedom, p=0.736.

Figure 31. Forest plot for ever versus never OC use (case-control and cohort studies, endometrial cancer incidence)



CI = confidence interval; OC = oral contraceptive

Sensitivity Analyses

We conducted an additional analysis to assess the impact of study quality; results were similar when including only the four good- and two fair-quality studies (OR 0.56; 95% CI, 0.43 to 0.74). We also explored how our findings changed when including only U.S.-based studies in our quantitative synthesis. Only one study was conducted with patients from the United States; the results of this study reported a somewhat greater protective effect than summary estimates for all studies (OR 0.34; CI, 0.25 to 0.47).

Duration of OC Use

Eight studies[37,138,155,156,250,252-254] were included in this meta-analysis examining the effect of duration of use on endometrial cancer incidence (Table 37). Of these, three were case-control studies and five cohort studies; five were rated good quality, two fair quality, and one poor quality. We excluded one study that did not report duration of use estimates.

Table 37. Data for outcomes on duration of OC use (endometrial cancer incidence)

Study	Duration	OR	95% CI
Case-Control			
Parslov, 2000[250]	< 1 yr 1–5 yr > 5 yr	0.4 0.2 0.2	0.3 to 0.7 0.1 to 0.3 0.1 to 0.4
Tao, 2006[254]	< 6 mo 6–23 mo 24–72 mo > 72 mo	0.94 0.74 0.75 0.50	0.64 to 1.38 0.50 to 1.09 0.52 to 1.07 0.30 to 0.85
Urban, 2012[155]	< 5 yr ≥ 5 yr	1.57 0.64	0.72 to 3.41 0.27 to 1.51
Cohort			
Vessey, 2006[156]	≤ 48 mo 49–96 mo ≥ 97 mo	0.6 0.4 0.1	0.3 to 1.1 0.2 to 0.8 0 to 0.4
Hannaford, 2007[37]	< 48 mo 49–96 mo > 97 mo	0.60 0.14 0.57	0.30 to 1.21 0.03 to 0.58 0.27 to 1.19
Setiawan, 2007[253]	< 5 yr ≥ 5 yr	0.96 0.60	0.71 to 1.30 0.39 to 0.91
Rosenblatt, 2009[138]	1–11 mo ≥ 12 mo	1.15 0.48	0.65 to 2.01 0.27 to 0.85
Dossus, 2010[252]	2–4 yr 5–9 yr ≥ 10 yr	1.06 0.66 0.58	0.79 to 1.41 0.47 to 0.91 0.42 to 0.79

CI = confidence interval; mo = month/months; OR = odds ratio; yr = year/years

For the included studies, we categorized duration of use into 2 intervals: (1) 1 to 60 months and (2) greater than 60 months. The results of this analysis, summarized in Table 38, show a time-dependent relationship as a function of duration. The duration trend was strong, and the two odds ratios were significantly different (p=0.007). There was significant heterogeneity, with a t-value of 4.39 for 7 degrees of freedom, p=0.003.

Table 38. Estimated odds ratios by duration of OC use (endometrial cancer incidence)

Duration	Odds Ratio (95% Confidence Interval)	P-value
< 60 months	0.78 (0.54 to 1.15)	0.162
> 60 months	0.44 (0.29 to 0.65)	0.002

OC Use and Endometrial Cancer Mortality

We identified two studies that evaluated the association between OC use and endometrial cancer mortality (Table 39).[33,165] Both were cohort studies, rated fair quality, and were conducted in the United Kingdom. Both studies demonstrated a strong, significant protective effect for endometrial cancer mortality associated with having ever used OCs. Results also showed a trend

of a greater protective effect associated with longer duration of use; however, the number of subjects within each category was small and point estimates for some duration categories were not calculable.

Table 39. Study characteristics and association between OC use and endometrial cancer mortality

Study	Study Details	Point Estimate (95% CI)[a]	Duration of Use	Point Estimate (95% CI)[b]	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort								
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–NR	0.43 (0.21 to 0.88)	< 4 yr 4–8 yr ≥ 8+ yr	0.9 (0.3 to 2.5) Not calculable 0.2 (0.0 to 1.0)	Age, parity, smoking, social class	UK	Fair	1
Vessey, 2010[165]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study 602,700 person-yr (total for exposed and unexposed) Recruitment period: 1968–1974	0.3 (0.1 to 0.8)	< 48 mo 49–96 mo ≥ 97 mo	0.42 (0.05 to 3.45) Not calculable Not calculable	Age, parity, BMI, smoking, social class	UK	Fair	1

BMI = body mass index; CI = confidence interval; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Point estimate for meta-analysis of ever versus never OC use.

[b]Point estimate for meta-analysis of duration of OC use.

[c]Meta-analysis code: 1 = Met inclusion criteria for possible meta-analysis.

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Strength of Evidence for OC Use and Risk of Endometrial Cancer

We graded the SOE for the association of ever use of OCs and risk of endometrial cancer as moderate (Table 40). We were able to quantitatively synthesize results across six studies. Results consistently showed a protective effect for ever use of OCs and the majority of studies were of good or fair quality. Confidence intervals displayed a satisfactory level of precision. Future studies may further improve precision but the overall magnitude of effect is unlikely to shift significantly.

We graded the SOE as low for the association between duration of OC us and endometrial cancer incidence. We found significant heterogeneity and confidence intervals were wide, decreasing precision. Future studies will likely impact the magnitude of effect but not the direction.

The SOE for endometrial cancer mortality and OC use was graded as moderate. We identified two large cohort studies that reported consistent results. Future studies may improve estimates of the magnitude of the effect but not the direction of effect.

Table 40. Strength of evidence domains for the effect of OC use on endometrial cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Endometrial Cancer in Overall Population						
Ever vs. never use	7 (308,198 across 4 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Precise	Moderate 0.57 (0.43 to 0.76)
Duration of use	8 (352,915 across 5 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Imprecise	Low <60 months:0.78 (0.54 to 1.15) >60 months: 0.44 (0.29 to 0.65)
Mortality						
Ever vs. never use	2 (46,112 in 1 study and 602,700 person-years in 1 study)	Medium	Consistent	Direct	Precise	Moderate Overall protective effect for ever use which is greater for longer durations of use

CI = confidence interval; SOE = strength of evidence

Discussion

Our study complements the prior literature by limiting the scope to studies conducted after 1999 in order to minimize the influence of older OC formulations that are no longer available on the U.S. market—thus potentially increasing generalizability for current clinical practice. In this systematic review and meta-analysis, we found that OC use is associated, to a varying degree, with breast, cervical, colorectal, and endometrial cancers. Below, we synthesize the main results for each cancer and compare to other contemporary reviews. We then highlight limitations of this review and areas for future research. Note that we found no evidence for publication bias in any of the meta-analyses (Appendix E).

Breast Cancer

The role of reproductive factors on the risk of developing breast cancer has been a topic of much study and debate. Thus, we sought to synthesize the evidence on the role of OCs on breast cancer incidence and mortality. We were able to pool results from 23 studies involving 356,023 women across 20 studies and 3,981,072 person-years across 3 studies that examined the effect of ever versus never OC use on the incidence of breast cancer. We found that the risk of breast cancer was slightly—but significantly—elevated for women who ever used OCs compared with women who never used OCs (OR 1.08; 95% CI, 1.00 to 1.17). A similar effect was seen among BRCA mutation carriers, although the results were not statistically significant (OR 1.21; CI, 0.93 to 1.58). (Although the inclusion of 1.0 in the 95% CI is considered nonsignificant using traditional rules of statistical inference, it is worth noting that the likelihood of the risk truly being increased when the lower bound is 1.0 is approximately 97.5%, and at a lower bound of 0.99, it is above 95%). Thus, as with ovarian cancer, the qualitative effect of OC use on breast cancer risk appears similar whether or not a BRCA gene mutation is present.

We found no time-dependent relationship as a function of duration of OC use across 14 pooled studies. Our duration of use results should be interpreted with caution; there was significant heterogeneity and the test was underpowered—which is not surprising, given that breast cancer is relatively uncommon during the ages when women are most likely to be using OCs. We did find a significant relationship with time since last OC use: women with more recent use had an elevated risk of breast cancers, with decreasing risk over time, so that by 10 years since last use, the risk among users was equivalent to never users. We did not identify sufficient studies meeting our inclusion criteria to calculate risk by age at first use. One collaborative reanalysis demonstrated an elevated risk of breast cancer for women who initiated use before age 20, an effect that diminished over time since last use.[182] We also found no evidence of increased breast cancer mortality associated with having used OCs compared with never use across four pooled studies.

Our results are consistent with the results of other meta-analyses and pooled analyses that identified a small increase in the relative risk of breast cancers associated with having ever used OCs, a risk that diminishes over time since last use.[182,255] The Collaborative Group on Hormonal Factors in Breast Cancer, a collaborative reanalysis of individual data in 153,536 women, found a small significant increase in the relative risk of breast cancers (OR 1.07 ± 0.02).[182] Similar to our results, the Collaborative Group did not identify an increase in risk with increasing duration of use or after discontinuation of use for 10 or more years. Another more recent meta-analysis of premenopausal breast cancers across 37 studies found a somewhat larger increase in the risk of breast cancer with the use of OCs (OR 1.19; CI, 1.09 to 1.29) with the greatest risk associated

with use of OCs prior to first full-term pregnancy (OR 1.44; CI, 1.28 to 1.62).[52] These results provide support for our finding that recent use (within 5 or fewer years) is associated with an increased risk of breast cancers. Women who delay first full-term pregnancies may also be more likely to be recent users of OCs relative to a breast cancer diagnosis. However, these results cannot be directly compared with ours, as this meta-analysis was restricted to premenopausal women or women younger than age 50 who may be at elevated risk due to other factors (e.g., genetic mutations) or represent cancer subtypes that differentially affect younger women. No pooled analyses or meta-analyses have assessed the excess risk of breast cancer mortality associated with OC use. However, our findings of an increased incidence, but no significant change in overall mortality, suggest that some of the increase in breast cancer incidence may be due to increased surveillance in women who use OCs. Women who use OCs must come in contact with the health care system on a regular basis, thus increasing their chances of receiving referrals for preventive screenings such as mammography. Another potential explanation would be an OC-induced change in the natural history of breast cancer or an increase in ER-positive breast cancers, which have higher survival, resulting in improved survival. Although the relative increase in breast cancer risk is small, the relative frequency of breast cancer diagnosis means that OC use may contribute to a substantial number of cases, an issue that is explored further in Section 5.

Cervical Cancer

While persistent infection with oncogenic HPV types has been identified as the necessary cause for the overwhelming majority of cancers of the cervix, it is not sufficient; OC use may represent an important cofactor. We identified 12 studies that assessed the risk of cervical cancer associated with OC use. Pooled results across 9 studies (representing 5,436 women across 6 studies and 3,981,072 person-years across 3 studies) found no significant increase in the risk of cervical cancer among ever users of OCs compared with never users. We also did not find a time-dependent relationship as a function of duration of OC use on cervical cancer. It is important to note that this contrast was underpowered with only five included studies. However, women who had long-term use of OCs (5 or more years) were at an elevated risk of cervical cancer compared with never users. Three studies (with 2592 subjects) assessed OC use and cervical cancer incidence among HPV-positive women. Results were similar to those of women not selected for HPV status. We only identified two studies that assessed the risk of cervical cancer mortality; results were mixed. Many studies did not control for factors that may influence risk, such as age at first OC use by duration or age at sexual debut, which is likely highly correlated with age at first use. Future research is needed to assess the additional cervical cancer risk associated with OC use among HPV-positive women. However, both studies reported statistically significant increased risk of death with 8 or more years of OC use compared with never use.

Results of this review differ in some ways from other evidence syntheses published over the last 10 years. Smith et al.[50] pooled study-level data across 28 studies and found an overall significant increase in the risk of cervical cancer when comparing ever versus never users of hormonal contraceptives (RR 1.2; 95% CI,1.1 to 1.3). We found a similar increase in the risk of cervical cancers, but our summary estimate was not significant. Both our review and the Smith et al. study found the risk of cervical cancer increased with prolonged exposure. This effect weakened but remained significant when stratifying duration by time since use. For our review, this effect was only significant for women who used OCs for 5 or more years compared with

never users; we did not have sufficient studies to stratify by time since last use. The International Collaborative of Epidemiological Studies of Cervical Cancer undertook a collaborative patient-level reanalysis of 24 observational studies.[49] Results expand the duration by recency effect. The collaborative analysis found that excess risk of cervical cancers increase with duration of use, but this effect declined after discontinuing OCs and was equivalent to the risk of nonusers after 10 years of nonuse.

There are key methodological differences between our study and the two recent syntheses that preclude drawing exact comparisons. First, we only included studies of invasive cervical cancers; the other studies also included carcinoma in situ and cervical intraepithelial neoplasia grade 3 (CIN 3). It is likely that effects differ between invasive cancers and cancer-precursor lesions. In fact, a case-case comparison in the collaborative reanalysis demonstrated significant differences in the risks for in situ and invasive cervical cancers for nearly every category of time since last use by duration of use.

Second, we only included studies assessing the effects of *oral* contraceptives or presented those data separately; the two other recent syntheses included all forms of hormonal contraceptive. It is also possible that formulation differences contribute to some of the differences we found between our results and their findings. However, the collaborative reanalysis reported separate findings for progestogen-only injectable contraceptives and found a similar pattern to those reported for OCs.

Third, we did not include the three identified studies conducted with women selected for HPV infection status. The effects of this decision appear to be negligible; both prior reviews noted similar patterns of findings when controlling for HPV status as a covariate[50] compared with HPV uncontrolled studies or among the subset of women with a confirmed HPV infection compared with populations not selected for HPV status.[49]

Fourth, we data-limited our search from 2000 forward in order to minimize the effect of older formulations that are no longer on the market; the other studies had no such date restrictions. Despite these differences, we found similar patterns of increased risk by duration of use. There is no direct evidence to suggest that cervical cancer screening recommendations should be different based on duration of OC use.

Colorectal Cancer

Many studies have suggested a protective effect of reproductive factors such as OCs on colorectal cancer risk. We identified 11 studies involving 503,816 women across 8 studies and 2,969,189 person-years across 3 studies that assessed the risk of colorectal cancers associated with the use of OCs. We found that the risk of colorectal cancer was significantly decreased for women who had ever used OCs compared with women who never used OCs (OR 0.86; CI, 0.79 to 0.95). However, we found no evidence of a time-dependent relationship as a function of duration. We found no significant heterogeneity. Duration results should be interpreted with caution; the test was underpowered. We had insufficient studies to assess a trend based on time since last use. We also identified two population cohort studies that assessed burden of colorectal cancer mortality associated with OC use. Results were mixed and neither study achieved statistically significant findings. The other study showed an increase in colorectal cancer mortality associated with having ever used OCs. Both studies also assessed mortality as a function of duration of OC use; results showed no clear trend of a greater protective effect associated with longer duration of use.

Our results are similar to two other evidence syntheses that also assessed the risk of colorectal cancers associated with OC use.[55,56] These meta-analyses both found a pooled relative risk of approximately 0.82, which is comparable to our pooled findings. These reviews also found no increase in the protective effect by duration of use. The similarity between our finding and those of the other two reviews is noteworthy. We limited our studies from January 2000 forward so that we had a greater probability of capturing a set of studies with newer OC formulations that may confer differential effects. Thus, we shared no studies in common with the Fernandez et al. study,[55] excluded 12 older or non-English studies, and included five newer studies[88,156,244,247,249] compared with the systematic review by Bosetti et al.[56] Similarity in our findings with these earlier evidence syntheses suggest that newer formulations of OCs still confer a significant protective effect for colorectal cancer and future research may be conducted to investigate its potential as a beneficial therapy for chemoprevention.

Endometrial Cancer

Estrogen and progestin both influence cell proliferation of endometrial tissue. Thus, we summarized the evidence on the use of OCs and risk of endometrial cancer incidence and mortality. We identified nine studies that evaluated the association between OC use and the incidence of endometrial cancers; seven studies were included in our meta-analysis to assess the effects of ever versus never use of OCs and represented 308,198 women across 4 studies and 3,981,072 person-years across 3 studies We found a significant protective effect associated with having ever used OCs (OR 0.57, 95% CI, 0.43-0.76). We also found a time-dependent relationship as a function of duration categorized as less than 60 months and 60 months or greater of total use. The duration trend was strong; however, the comparison of the two odds ratios was not significant, and heterogeneity limits conclusion about this analysis.

Our study is one of the few systematic reviews and meta-analyses to summarize the evidence on the effects of OCs on endometrial cancers. Grimes et al.[256] conducted a systematic review and qualitative synthesis of studies up to 1993. They identified 13 case-control studies with protective odds ratios ranging from 0.1 to 0.6, with most effects clustering around 0.5 (CI not reported). Two of the three cohort studies identified also found protective effects of OC use on endometrial cancer incidence. Schlesselman et al.[257] conducted a meta-analysis of 11 case-control studies. A significant duration trend was reported such that longer durations of use conferred greater protection against endometrial cancers (RR 0.44 for 4 years of use; RR 0.33 for 8 years of use; RR 0.28 for 12 years of use; $p<0.0001$). We found a similar trend but used a different analytic approach; direct comparisons are difficult to draw. This meta-analysis also reported on time since last use and found that the protective effect of OCs is diminished after they are discontinued but still persists even 20 years after cessation of use. We did not have sufficient studies to assess the effect of time since last use. Protective effect of OCs may vary with formulation. However, our results are similar to other studies conducted in the 1990s that may have included different formulations based on market availability. Our results—in combination with other evidence reviews—confirm that OCs confer a significant and lasting protective effect on the risk of endometrial cancers.

Issues Related to Cancer Screening

Of the five cancers considered in this report, effective screening is available for three: breast, cervical, and colorectal cancers. Differential screening behaviors among OC users and nonusers may affect both incidence and mortality, depending on the cancer targeted by screening.

As previously discussed, there are no effective screening tests for ovarian cancer, and although screening is possible for endometrial cancer, screening is not recommended outside of certain high-risk groups. Thus, the observed decrease in incidence and mortality for both cancers cannot be related to screening. However, as shown in Table 41, there is potential for confounding by variations in screening behaviors for the other cancers. This may be particularly important in U.S.-based studies, where there is much greater variation in access to screening, and where reproductive health services, including contraceptive services, have traditionally been closely linked with preventive care. Breast cancer screening primarily detects early malignancies, rather than preinvasive disease. Screened women will have a higher incidence (particularly at younger ages), but lower mortality, since effective treatment is available for many of these early malignancies. This is similar to the pattern observed in OC users, suggesting that some of the effects may be related to differential screening.

Conversely, cervical and colorectal cancer screenings detect both premalignant lesions and early cancers, leading to both decreased incidence and mortality. The observed protective association between OC use and colorectal cancer is consistent with this effect. However, the increased incidence associated with cervical cancer is in the opposite direction from any potential screening bias.

Table 41. Variation in screening behaviors by cancer type and potential confounding on incidence and mortality estimates

Cancer Type	Screening Detects		Predicted Effect if OC Users More Likely To Be Screened		Observed Effect in OC Users	
	Preinvasive Disease	Early Invasive Disease	Incidence	Mortality	Incidence	Mortality
Breast	No	Yes	Increased	Decreased	Increased	Uncertain
Cervical	Yes	Yes	Decreased	Decreased	Increased	Increased
Colorectal	Yes	Yes	Decreased	Decreased	Decreased	Uncertain
Endometrial	No screening	No screening	None	None	Decreased	Decreased
Ovarian	No screening	No screening	None	None	Decreased	Decreased

OC = oral contraceptive

Limitations

While we performed a comprehensive systematic review and evidence synthesis of the current research on OCs and breast, cervical, colorectal, and endometrial cancer, there are limitations to our approach and findings. First, as expected, we identified no randomized trials. Such studies are likely not feasible. Thus, we only included case-control, cohort, and pooled observational studies in our meta-analyses. Even the highest quality observational studies are susceptible to multiple forms of bias. The majority of studies in this review were rated good quality or fair quality as observational studies. Sensitivity analyses restricted to only good and fair studies found similar patterns of results.

Second, confounding is also another major limitation of observational studies. Again, most included studies adjusted for multiple likely sources of cofounding. When possible, we used the most adjusted point estimates in our meta-analyses. However, these covariates were not consistent between studies. Recall bias is also a common source of diminished quality in observational studies. Our findings were remarkably similar across case-control studies and cohort studies, which suggests a lack of evidence for recall bias of OC use across study types.

Third, we found significant heterogeneity across many of our comparisons. There are multiple potential sources of this heterogeneity. We included a diverse group of studies conducted across the world; differences in study populations and geographic variability in other

risk factors not routinely assessed (e.g., access to health care) likely contributed to this heterogeneity. This may be particularly true for cancers such as breast, cervical, and colorectal where screening can affect both incidence and mortality, and where there may be associations between OC use and screening behaviors. Sensitivity analyses with only U.S.-based studies (or with patients from the United States) showed similar patterns to unrestricted analyses. Other potential sources of heterogeneity include change in patterns of OC use associated with delayed parity over the last 30 year, variable date of diagnosis, and change in OC formulations available on the market. While date limiting our review from 2000 forward likely diminished some of these sources of heterogeneity, this approach may not be adequate to control for these effects. Also, studies varied considerably in the type and specification of covariates across studies, which may be a likely source of heterogeneity.

Fourth, we found limited data on special populations. For breast cancer, we identified only three studies on the effect of OCs on women with family histories, only seven studies with BRCA1/2 carriers, and five studies related to subtypes of cancers. Studies with special populations for cervical, colorectal, and endometrial cancers were even more limited. Underlying risk factors related to family history or genetic mutation carrier status, tumor type, or health behaviors (e.g., smoking, obesity) may interact with OC use to attenuate or enhance effects. Thus, we are not able to make specific recommendations for specific populations.

Last, we date-limited our search to studies after 1999 in order to minimize the influence of older OC formulations that are no longer available on the U.S. market and increase generalizability for current clinical practice. However, study publication date is a gross estimate of OC formulation exposure since observational studies published after 1999 may still represent cohorts exposed to earlier formulations of OCs. It may have been preferable to limit studies on the basis of year of diagnosis than date of publication. However, many of our findings are consistent with other meta-analyses without date restrictions. This suggests that current OC formulations may have similar carcinogenic or protective effects compared with older formulations. However, given the long latent period between exposure and tumor development, recent publications may not fully assess the effect of formulations introduced in the past 20 years.

Future Research

This comprehensive review of the literature on the risk of breast, cervical, colorectal, and endometrial cancers associated with OC use identified several gaps in the current state of the evidence that warrant future investigation. We detail these gaps below.

Special Populations

Several subgroups deserve further attention. There are limited data on the effects of OCs on cancer risk in women at elevated risk due to behavioral risk factors such as smoking, heavy alcohol consumption, obesity, or physical inactivity. These factors are known to be associated with cancer development; therefore, behavioral risk factors may modify the association between OCs and cancers. Moreover, we found limited studies with women of known genetic predisposition. Either known gene mutations that predispose to cancer or a strong family history can increase women's chance of breast, endometrial and colon cancers. These subgroups deserve further study as to whether they have the same or different benefit from OC use. Also, cancer is not a homogeneous disease; thus, certain types of tumors may differently be affected by OC use. Futures studies should assess the effectiveness of OCs among cancer subtypes. While it is

unlikely and unfeasible that large randomized trials on the effect of OC use will be conducted, long-term prospective studies of adequate size could be beneficial in disentangling the effects of OC and cancer among special populations.

Interactions by Patterns of Use

Our findings demonstrate a statistically significant increase in breast cancer and a statistically significant decrease in colorectal and endometrial cancers for ever OC use versus never OC use. We found that duration of use conferred a different pattern of risks; however, we found limited support of a time-dependent relationship. These analyses were underpowered; we found significant heterogeneity. We also found limited data to assess a trend in time since last use, age at first use or age at last use. As the benefits and risks associated with OC use differ by pattern of use, more research is needed on the interaction of different patterns of use (e.g., duration by time since last use, age at initiation by duration) on the risk of breast, cervical, colorectal, and endometrial cancers in order to optimize the risks and benefits of OC use.

Newer OC Formulations

Our analyses were based on more recently published data than previous evidence syntheses; however, we found similar estimates associated with ever use. This suggests that the lower dose OCs that would have been used more commonly by those women included in more recently published studies confer similar effects than higher dose OCs on the risk of breast, cervical, endometrial, and colorectal cancers. However, continued investigation is needed. The long lag time for cancer development, and the potential for significant discrepancy between dates in which cohorts were assembled relative to publication dates, make it difficult to assess if we were successful in limiting this review to more modern formulations of OCs than prior evidence synthesizes. Thus, prospective studies with continued evaluation of effects by dose of OCs are warranted.

Population-based Mortality Studies

We found relatively few population-based studies that assessed the risk of breast, cervical, colorectal, and endometrial cancer mortality associated with OC use. Future research should continue to assess this relationship. Findings from both incidence and mortality studies are needed to assess if associations are related to enhanced or obstructed cell proliferation or screening uptake and adherence among OC users.

Patient-level Meta-analyses

Given the high levels of heterogeneity across comparisons, variability in measurement related to patterns of use, and limited data on special populations who may be differentially affected by the use of OCs, we acknowledge that a study-level meta-analysis may be inadequate to answer important questions in this area. Thus, patient-level meta-analysis may provide critical information to assess gaps related to interactions between patterns of use, effects by subpopulations, and specific estrogen and progestin formulations.

Study Design and Reporting

One step that would facilitate future systematic reviews would be standardization of categories and descriptive statistics for reporting results. While categorization choices will vary

for individual studies, reporting of standardized results, perhaps as an appendix to the main analysis, would greatly improve the ability to combine published results in meta-analysis.

Section 4. Oral Contraceptives and Vascular Events

Background

Oral contraceptives (OCs) are the most common form of birth control in the United States.[172] Over 10 million women aged 15 to 44 (17%) are current users of OCs, and 45 million women have used OCs at some time in their life ("ever users").

Since the 1960s, several life-threatening vascular events have been reported to be associated with OC use.[258] These include venous thromboembolic (VTE) disease (encompassing deep venous thrombosis [DVT] and pulmonary embolism [PE]), stroke, and myocardial infarction [MI]). Ischemic heart disease and stroke are the leading cause of death in the United States and worldwide, accounting for greater than 30 percent of all deaths.[259] Given the large number of women currently using OCs, an increased risk of such vascular events associated with OC use is an important public health issue.

Over the last several decades, formulations of OCs have drastically changed. Many formulations that were used by participants in earlier studies are no longer available. Most contemporary OCs contain lower doses of estrogen and new generations of progestins. Progestin-only OCs are also commonly prescribed. Women using progestin-only OCs, lower dose estrogen OCs, or OCs with newer progestins may experience modified risks of VTE, stroke, and MI compared with users of older OCs.[260,261] There are few studies focusing on the acute vascular risks associated with contemporary OC use. In addition, more information is needed to understand whether particular groups of women may be at heightened risk of VTE, stroke, or MI due to use of specific OC formulations or presence of thromboembolic risk factors.

In Section 4 of our systematic review and meta-analysis, we evaluate the association between contemporary OC use and the risks of developing VTE, stroke, or MI. We also investigate whether the risk of these acute vascular complications varies according to estrogen dose, progestin generation, or duration of OC use or among populations of women with elevated risk for thromboembolic events.

Relevant Key Questions

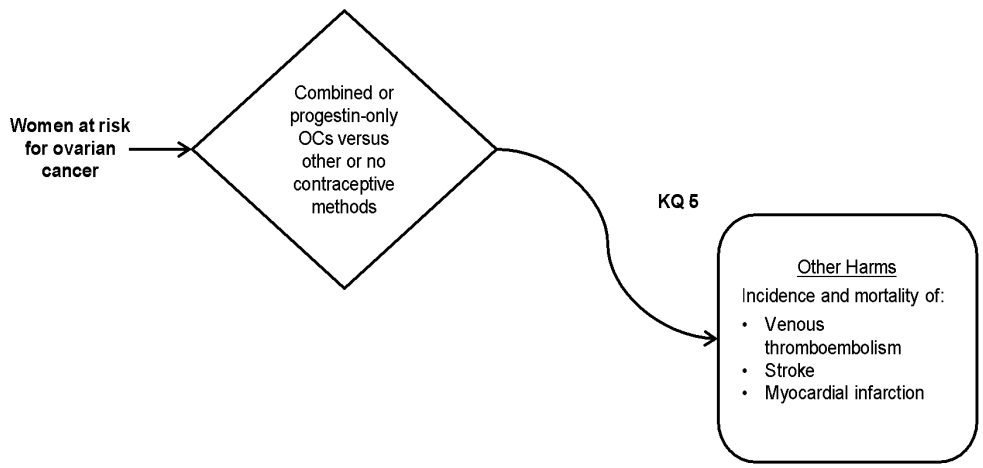
The seven KQs developed for the entire systematic review are listed in Section 1 (refer to Figure 7 for a roadmap of this report). For Section 4, we performed a systematic review and meta-analysis on the part of KQ 5 that addresses the acute vascular events associated with OC use; namely, VTE, stroke, and MI.

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

Analytic Framework

Figure 32 shows the analytic framework that guided this section of the review.

Figure 32. Analytic framework for OCs and vascular events



KQ = Key Question; OC = oral contraceptive

Methods

Inclusion and Exclusion by PICOTS

Table 42 describes the PICOTS criteria that guided the literature search for this section of the review.

Table 42. Summary of inclusion and exclusion criteria for OCs and vascular events

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• All KQs ○ Women taking OCs for contraception or women taking OCs for primary prevention of ovarian cancer[a] ○ Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy	Nonhuman studies
Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	Study does not provide a description of at least one of the following: (1) OC formulation(s) used (2) length of OC use

Table 42. Summary of inclusion and exclusion criteria for OCs and vascular events (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Study does not include non-OC controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable) or a comparison between OC formulations
Outcomes	Study reports quantitative association between exposure to OCs and either incidence or disease-specific mortality for any of the following: • Venous thromboembolic disease (including deep vein thrombosis or pulmonary embolus) • Stroke • Myocardial infarction	Study only reports outcomes related to assisted reproductive technologies or abortion
Timing	Studies of any duration	None
Setting	All settings	None
Study design	• Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] • Study sample size ≥ 100 subjects for nonrandomized studies[c]	• Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor) • Exploratory study with inadequate sample size
Publications	• English-language only • Peer-reviewed articles • Study reports venous thromboembolic event, stroke, or myocardial infarction outcome of interest and was published on or after 01-Jan-1995[d]	Non-English articles[e]

KQ = Key Question; OC = oral contraceptive

[a]If the purpose of OC use was unclear, it was assumed to be contraception.

[b]Systematic reviews and study-level meta-analyses were excluded from abstraction; those representing key sources were hand-searched as potential sources of additional material.

[c]Small nonrandomized studies <100 subjects were excluded as confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

[d]Date ranges for acute vascular events associated with OC use were restricted to more recent years to reflect currently available formulations.

[e]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies) and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Meta-Analytic Methods

To examine the effect of OCs on the risk of developing acute vascular complications, we analyzed the following relationships:

- Temporal relationships:
  - Current versus noncurrent OC use
  - Ever versus never OC use
  - Duration of current OC use
- OC formulation:
  - Estrogen dose (high versus low)

  - Progestin generation (first, second, third, and fourth generations)
- Special populations:
  - Blood-clotting disorders
  - Cardiovascular risk factors
  - Migraines

When study designs and outcomes reported were similar and the population in the study was broad (e.g., not Factor V Leiden carriers), we estimated pooled odds ratios with 95% confidence intervals (95% CIs) using a random-effects model. We evaluated heterogeneity visually and with the Cochran *Q* statistic using a threshold p-value of less than 0.10. We stratified analyses by study type (case-control, cohort, pooled analyses). All meta-analyses were performed using Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ; 2005).[68]

Confidence intervals from the included study publications were entered into the Comprehensive Meta-Analysis (CMA) program. However, many of these confidence intervals had been rounded to a single decimal place. The CMA program checks the intervals for symmetry in the logarithmic scale. In certain cases, the rounded limits were not accepted by CMA. In such cases, we kept the point estimate as given but changed the confidence limits so that they were symmetric. This resulted in slight differences in the confidence intervals in the forest plots when compared with the study publications.

Results were discussed qualitatively when study numbers were insufficient for meta-analysis, when confidence intervals around measures of association were not reported or could not be calculated, or when a study included a special population that is not likely to be representative of the general population of reproductive age women.

Pooled Analyses

We included pooled analyses in our meta-analyses if all three of the following conditions were met:

- None of the individual studies included in the pooled analysis had already been included for meta-analysis.
- At least half of the studies in the pooled analysis were published on or after January 1, 1995.
- Data in the pooled analyses were presented such that their inclusion in the current meta-analysis was feasible.

Temporal Relationships

Current OC Use

For prior sections of this report, the primary exposure to OCs was defined as ever use compared with never use of OCs. While the exact mechanisms responsible for the increased risk of VTE, stroke, or MI among OC users are unknown, there is evidence that the risk is increased in *current users* of OCs, with past users demonstrating either no risk or lower risk than current users of OCs.[262-265] Indeed, the majority of studies identified for these outcomes defined the primary exposure as current versus noncurrent OC use. Therefore, for Section 4, we defined the primary exposure as current use of OCs. Current use is defined as use within the year preceding the diagnosis of each outcome. The referent category was noncurrent use of OCs, which can consist of never users, former users, or both.

Ever OC Use

As noted above, our primary exposure was defined as current use (use within 1 year preceding diagnosis) rather than ever use as defined in the other sections.

Duration of OC Use

We were unable to perform meta-analyses for any of the outcomes of interest in relation to duration of OC use because there were too few studies to power the analysis. In order to have adequate power in the analysis, 20 or more studies would be needed for a particular outcome. The results of our included studies are therefore discussed qualitatively.

OC Formulation

All current OC formulations contain ethinyl estradiol, but the dose of this estrogen varies and may modify the risk of vascular events. We divided OC formulations by high-dose estrogen (assumed to be ≥50 mcg ethinyl estradiol) and low-dose estrogen (assumed to be <50mcg ethinyl estradiol). For estrogen dose formulation analyses, we included studies that compared the risks of developing VTE, stroke, or MI among current OC users by low versus high estrogen dose.

OC formulations were also categorized according to generation of progestin. Originally, progestins used in OCs were developed for their antigonadotropin effects leading to contraception. The resulting progestins also had effects on other steroid receptors including estrogen receptors, androgen receptors, glucocorticoid receptors, and mineralocorticoid receptors. Each progestin may increase or decrease the activity of these receptors, leading to various symptom profiles (acne, water retention, etc.). Newer progestins have been developed with a goal of not only preventing conception but also offering the best side effect profile: lighter bleeding, less acne, no bloating. Progestins have been classified in generations according to their appearance in the market and not on their chemical structure or interactions.[266] For the purpose of our analyses, first-generation progestins include norethindrone and ethynodiol diacetate; second-generation include levonorgestrel and norgestrel; third-generation include gestodene, desogestrel, and norgestimate; and fourth-generation include drospirenone, dienogest, and cytoproterone acetate. When an odds ratio was presented for a specific OC formulation, we included that odds ratio categorized by the generation of the progestin used.

Results

This section presents results of our detailed analysis of the relationship between OCs and acute vascular events, which include VTE (DVT and PE), stroke, and MI. Of note, no randomized controlled studies were identified for any of the outcomes of interest; therefore, the analyses are based on observational studies.

OC Use and Venous Thromboembolism Incidence

We identified 33 studies that evaluated the association between OC use and the incidence of VTE.[181,260-264,267-313] Of these studies, 20 were case-control studies and 14 were cohort studies; 10 studies were rated good quality, 21 fair quality, and 3 poor quality. Twenty-five studies assembled patient groups that were fully or partially based in Europe or the UK; only 7 included patients from the United States (Table 43).

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control							
Anonymous, 1995[181] Anonymous, 1995[268] Anonymous, 1998[267]	**Women aged 20–44 yr in WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception** Cases: 372 VTE, hospital Controls: 460 no VTE, hospital Recruitment period: 1990–1994	4.1	3.2 to 5.2	BMI, smoking, alcohol consumption, varicose veins, hypertension in pregnancy	Africa, Asia, Europe, Latin America	Good	1
Bloemenkamp, 1995[260] Bloemenkamp 2000[302]	**Consecutive women aged 15–49 yr with a first episode of proven DVT** Cases: 126 DVT, anticoagulation clinics Controls: 159 no DVT, source NR Recruitment period: 1988–1992	NR	NR	NA	Netherlands	Fair	2
Andersen, 1998[269]	**Women aged 18–49 yr in regional discharge summaries from 10 hospitals** *First- and second-generation users* Cases: 24 VTE (including PE), hospital Controls: 134 no VTE, blood donors *Third-generation users* Cases: 16 VTE (including PE), hospital Controls: 134 no VTE, blood donors Recruitment period: 1997–NR	5.2 48.6	1.6 to 16.4 5.6 to 423.0	Parity, BMI, Smoking	Denmark	Fair	1
Lidegaard, 1998[270]	**Women aged 15–44 yr in all hospitals in Denmark** Cases: 375 VTE, hospital registry Controls: 1041 no VTE, source NR Recruitment period: 1980–1993	NR	NR	NA	Denmark	Fair	2
Bloemenkamp, 1999[271]	**Women aged 15–49 yr in medical centers in Amsterdam** Cases: 185 VTE, hospital Controls: 591 no VTE, hospital Recruitment period: 1982–1995	3.9	2.6 to 5.7	Age, family history, center, calendar time	Netherlands	Good	1

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Lewis, 1999[261] Heinemann, 1999[272] Suissa, 1997[273] Suissa, 2000[274]	**Women aged 16–44 yr in Transnational Study on Oral Contraceptives and the Health of Young Women** Cases: 505 VTE, hospital Controls: 2270 no MI, thromboembolic CVA, or VTE, hospital and community Recruitment period: 1993–1996	2.90	2.06 to 4.09	Age, BMI, smoking, alcohol use, duration of use by generation, duration of previous use by generation, switching by generation	Austria, France, Germany, Switzerland, UK	Fair	1
Todd, 1999[299]	**Women aged 15–49 in the UK MediPlus database** Cases: 106, idiopathic VTE, registry Controls: 569, no VTE, registry Recruitment period: 1992–1997	NR	NR	NA	UK	Fair	2
Jick, 2000[296]	**Women aged 15–39 yr taking third-generation OCs or OCs with levonorgestrel** Cases: 99, VTE, registry Controls: 366, no VTE, registry Recruitment period: 1993–1999	NR	NR	NA	UK	Good	2
Spannagl, 2000[275]	**Women aged 15–49 yr in population-based cohort study** Cases: 80 VTE including PE, from cohort study Controls: 406 no VTE or PE, from cohort study Recruitment period: 1995–1997	3.0	1.8 to 5.0	BMI, varicose veins, family history of VTE	Germany	Poor	1
Lidegaard, 2002[276]	**Women aged 15–44 in national patient registry** Cases: 987 VTE including PE, registry Controls: 4054 Recruitment period: 1994–1998	NR	NR	NA	Denmark	Good	2

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Legnani, 2002[277]	**Women aged 15–68 with specific genetic mutations** Cases: 301 VTE including PE, hospital Controls: 650, population Recruitment period: 1994–2000	NR	NR	NA	Italy	Fair	2
Legnani, 2004[278]	**Women aged 15–68 yr with specific genetic mutations** Cases: 195 VTE including PE, hospital Controls: 488, population Recruitment period: 1994–2000	NR	NR	NA	Italy	Fair	2
Sidney, 2004[262]	**Members of California Kaiser Permanente Medical Care Program aged 18–44 yr** Cases: 196 VTE hospital and administrative records Controls: 746, hospital and administrative records Recruitment period: 1998–2000	2.99	1.86 to 4.81	Age	U.S.	Good	1
Jick, 2006[298]	**Women aged 15–39 yr in the PharMetrics database who were prescribed OCs containing norgestimate, desogestrel, or levonorgestrel** Cases: 281 VTE including PE, registry Controls: 1055, registry Recruitment period: 2000–2005	NR	NR	NA	U.S.	Fair	2

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Huerta, 2007[264] Farmer, 2000[279]	**Women aged 20–79 yr in UK General Practice Research Database** ***VTE*** Cases: 197 VTE, registry Controls: 788, no VTE, registry *DVT* Cases: 122 DVT, registry Controls: 788, no DVT, registry *PE* Cases: 75 PE, registry Controls: 788 no PE, registry Recruitment period: 1994–NR	1.85 2.05[c] 1.56[c]	1.38 to 2.48 1.46 to 2.89 1.04 to 2.35	Age, BMI, smoking, calendar year, cancer, fractures in last month, surgery in last 6 mo, use of warfarin sodium, visits to family physician in last yr	UK	Good	1
Austin, 2009[280]	**African-American women aged 18–49 yr** Cases: 60 DVT or PE, hospital Controls: 196 no DVT or PE, outpatients Recruitment period: NR	2.8	1.4 to 5.7	Age	U.S.	Fair	1
Van Hylckama Vlieg, 2009[281]	**Women <50 yr in anticoagulation clinics MEGA study** Cases: 1524 DVT or PE, anticoagulation clinic Controls: 1760 no DVT or PE, partners of cases Recruitment period: 1999–2004	4.39[d]	3.87 to 5.09	Age, period of inclusion	Netherlands	Good	1
Barsoum, 2010[282]	**Rochester Epidemiology Project, age NR** Cases: 726 VTE, registry Controls: 830 no VTE, registry Recruitment period: 1988–2000	4.03	1.83 to 8.89	BMI, "previously identified risk factors"	U.S.	Good	1

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Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Dinger, 2010[283]	**Women aged 15–49 in survey of primary care and specialty physicians** Cases: 680 DVT or PE, outpatients Controls: 2720 no DVT or PE, outpatients Recruitment period: 2002–2008	2.4	1.8 to 3.2	Parity, BMI, family history, smoking, personal history of VTE, duration of OC use, education, chronic disease, concomitant medication	Germany	Fair	1
Heinemann, 2010[284]	**Women aged 15–49 yr in survey of physicians, and registry** Cases: 434 DVT or PE, outpatients and registry Controls: 1920 no DVT or PE, community Recruitment period: 2002–2006	NR	NR	NA	Austria	Good	2
Jick, 2011[312]	**Women aged 15–44 yr in the PharMetrics database in the U.S.** Cases: 186 OC users with VTE, registry Controls: 681 OC users and no VTE, registry Recruitment period: After 2001	NR	NR	NA	U.S.	Fair	2
Parkin, 2011[300]	**Women aged 15-44 yr in UK General Practice Research Database** Cases: 61 VTE, registry Controls: 215 no VTE, registry Recruitment period: 2002–2009	NR	NR	NA	UK	Fair	2

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
			Cohort				
Farmer, 1995[285]	**Women aged 14–45 registered with participating general practices in the UK** Exposed: 111,449 person-years Unexposed: 542,906 person-years Recruitment period: 1990–1991	NR	NR	NA	UK	Fair	2
Grodstein, 1996[286]	**Women ≥30 yr in Nurses' Health Study** Exposed: 731,326 person-years Unexposed: 829,240 person-years Recruitment period: 1976–1992	2.2	0.8 to 5.9	Age, parity, BMI, smoking, postmenopausal hormone use, diabetes, high blood pressure, high cholesterol, time period	U.S.	Fair	1
Farmer, 1997[287]	**Women aged 15–49 in General Practice Research Database** Exposed: 234,899 Unexposed: NR (database includes ~1.1 million women) Recruitment period: 1992–1997	NR	NR	NA	UK	Fair	2
Hannaford, 1998[288]	**Royal College of General Practitioners' (RCGP) Oral Contraception Study** *DVT* Exposed: 335,181 person-years Unexposed: 228,727 person-years *PE* Exposed: 335,181 person-years Unexposed: 228,727 person-years Mean age at study entry: 49 Recruitment period: 1968–NR	1.6 1.56	1.25 to 2.04 1.14 to 2.14	Age, parity, smoking, social class	UK	Poor	1

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort (continued)							
Herings, 1999[301]	**Women aged 15-49 yr in eight Dutch cities** Exposed to 3rd generation progestins: 29,986 person-years Exposed to 2nd generation progestins: 24,953 person-years Recruitment period: 1986–1995	NR	NR	NA	Denmark	Fair	2
Conard, 2004[289]	**Women aged 15–50 yr in Hemostasis and Thrombosis Unit** Exposed: 102 Unexposed: 102 Recruitment period:1992–1997	0.8	0.2 to 3.9	Age, BMI, thrombophilia	France	Fair	4
Samuelsson, 2004[290]	**Women aged 15–44 yr in hospital in Jamtland** Exposed: 43 Unexposed: 32 Recruitment period: 1991–2000	NR	NR	NA	Sweden	Fair	2
Dinger, 2007[297]	**Women in the EURAS study** Exposed: 16,534 prescribed DRSP-containing OCs Unexposed: 26,341 prescribed other OCs Recruitment period: 2000–2004	NR	NR	NA	Austria, Belgium, Denmark, France, Germany, Netherlands, UK	Good	3
Seeger, 2007[291]	**Women aged 10–59 yr in health insurance database** Exposed: 22,429 Unexposed: 4858 Recruitment period: 2001–2004	NR	NR	NA	U.S.	Fair	2
van Vlijmen, 2007[292]	**Women aged 15–50 yr in specialty clinic** Exposed: 135 Unexposed: 87 Recruitment period: NR	9.7	3.0 to 42.4	Clustering of women within families	Netherlands	Fair	4

Table 43. Study characteristics and association between OC use and venous thromboembolism incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort (continued)							
Gronich, 2011[311]	**Women aged 12–50 yr in a health care plan in Israel** Exposed: 431,223 use episodes. Total of 819,749 woman-years of followup Recruitment period: 2002–2008	NR	NR	NA	Israel	Fair	2
Lidegaard, 2011[293]	**Women aged 15–49 yr in national registries** Exposed: 2,821,686 person-years Unexposed: 4,960,730 person-years Recruitment period: 1995–2005	2.83	2.65 to 3.01	NA Age, calendar year, education level	Denmark	Fair	1, 2
Le Gal, 2010[294]	**Women >18 yr in 12 thrombosis clinics** Exposed: 49 Unexposed: 247 Recruitment period: 2001–2006	0.6	0.1 to 2.8	Age	U.S., Canada, France, Switzerland	Fair	4
van Vlijmen, 2011[295]	**Female relatives from 4 family cohorts (first-degree relatives of consecutive patients with VTE or premature atherosclerosis)** Exposed: 571 Unexposed: 227 Recruitment period: 1995–2004	2.1	1.1 to 4.1	Pregnancy and clotting defects	Netherlands	Fair	4

BMI = body mass index; CI = confidence interval; DRSP = drospirenone; DVT = deep venous thrombosis; mo = month/months; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; PE = pulmonary embolism; UK = United Kingdom; U.S. = United States; VTE = venous thromboembolism; WHO = World Health Organization; yr=year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Meta-analysis code: 1 = Included in this meta-analysis of current versus noncurrent OC use; 2 = Excluded due to current versus noncurrent OR not reported or not calculable; 3 = Excluded due to progesterone-only OC use; 4 = Excluded due to family history of VTE or thrombophilia.

[c]This odds ratio is not included in the meta-analysis because it represents a subset of the total VTE population (OR=1.85).

[d]Calculated by pooling the ORs of individual subgroups.

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Current Versus Noncurrent OC Use

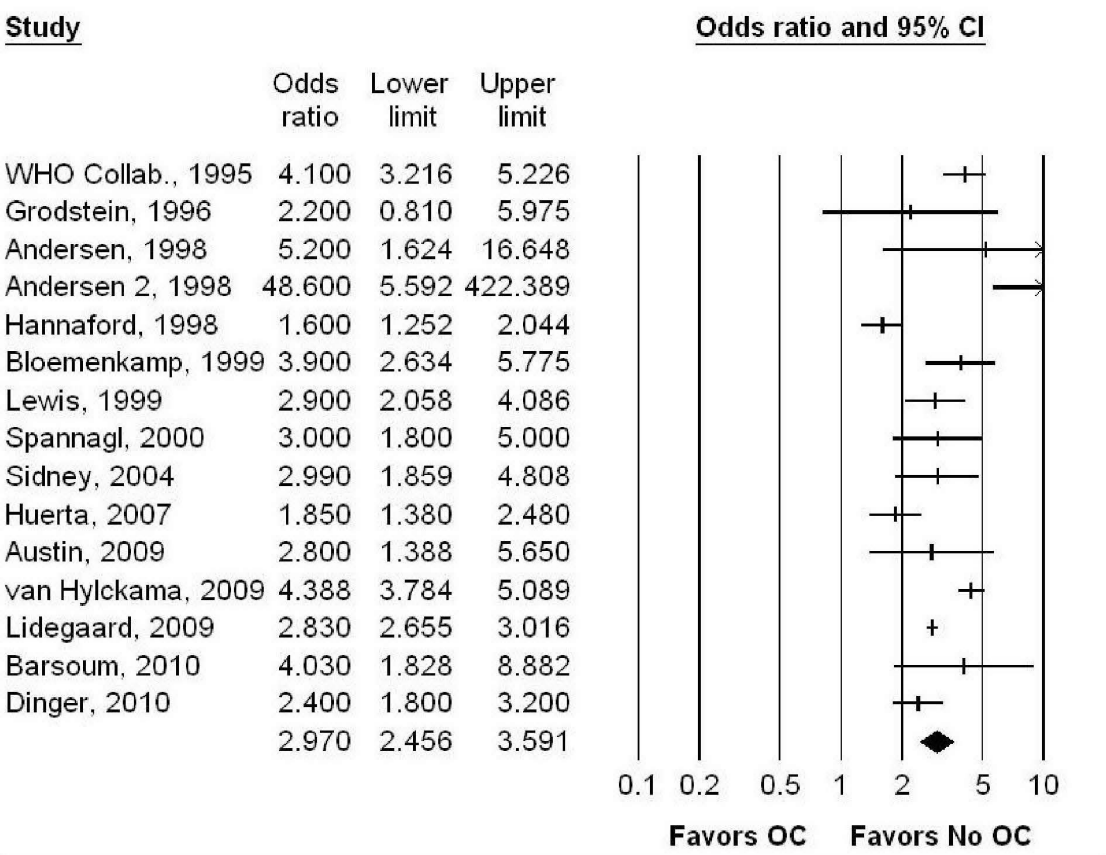
Fourteen studies[261-264,268,269,271,275,280-283,286,288] were included in this meta-analysis examining the effect of current versus noncurrent OC use on VTE incidence. Of these, 11 were case-control studies representing a combined 4565 cases and 10,901 controls; and 3 were cohort studies representing 3,888,193 exposed person-years and 6,018,697 unexposed person-years. Six studies were rated good quality, 6 fair quality, and two poor quality (Table 43). Only four studies in this meta-analysis included patients from the United States.[262,280,282,286]

In addition to the 14 studies included in the meta-analysis, a recently published, good-quality study[293] reported relative risks of VTE associated with several different progestin formulations compared with no OC use. The data from this important study were not included in the meta-analysis so as not to inappropriately pool odds ratios with adjusted relative risks, with the latter calculated based on person-years of exposure. This study also included patients from an earlier publication by Lidegaard et al.[263] Data from the earlier study are included in the meta-analysis. The study by Andersen et al.[269] contributed two ratio measures because the risk was only reported separately by progestin generation. The VTE outcome included PE and DVT in the majority of studies. One study[286] included only PE cases. The comparison groups for noncurrent OC users was (1) never users in six studies, (2) former and never users in seven studies, and (3) unspecified in one study.

Abstracted data not included in this meta-analysis are specified (with rationale) in Table 43. Reasons for exclusion from this analysis included the following: no reporting of odds ratios for current versus noncurrent OC users;[260,277,278,284,285,287,290,291,296,298-301,311,312] family history of VTE or thrombophilia in control group and cases;[289,292,294,295] and only including progesterone only OCs.[297]

Figure 33 shows the random-effects meta-analysis of the 14 studies. The result is an estimated odds ratio of 2.97 (95% CI, 2.46 to 3.59), demonstrating a significant increase in VTE risk with current OC use. There was significant heterogeneity, with a Q-value of 82.207 for 14 degrees of freedom, $p<0.001$.

Figure 33. Forest plot for current versus noncurrent OC use and the risk of VTE



CI = confidence interval; OC = oral contraceptive
Note: the study by Andersen (1998) contributed two ratio estimates because the risk was reported separately by progestin generation.

Sensitivity Analyses

We performed sensitivity analyses by excluding studies that did not include patients from the United States. The odds ratio for the remaining four studies was essentially unchanged from the larger analysis (OR, 3.00; 95% CI, 2.15 to 4.19). A second sensitivity analysis excluded the two poor-quality studies and resulted in a similar OR of 3.17 (95% CI, 2.62 to 3.83).

Ever Versus Never OC Use

One cohort study[288] examined the effect of ever versus never OC use on the risk of VTE. The risks of DVT and PE were significantly increased in ever versus never users with a risk ratio of 1.56 (95% CI, 1.14 to 2.14) for PE and 1.66 (95% CI, 1.25 to 2.04) for PE. However, these "ever users" included current and past users.

Three studies represented in the current versus noncurrent meta-analysis[262-264] stratified ever users by current and former users to examine whether current versus ever use conferred different risk for VTE. In all three studies, the odds of developing VTE were significantly increased among current users. However, one case-control study[262] found no difference in the odds of VTE

for ever versus never users (OR, 1.25; 95% CI, 0.78 to 2.01) and no difference in the odds of VTE for former versus never users (OR, 0.73; 95% CI, 0.44 to 1.21). A second case-control study[264] found only slightly increased odds of PE for former versus never users (OR 1.27; 95% CI, 1.08 to 1.49) but no difference in the odds of DVT (OR 1.14; 95% CI, 0.98 to 1.34). The cohort study[263] found no increased odds of VTE among former versus never users (OR 1.08; 95% CI, 0.98 to1.18). We did not conduct a meta-analysis of ever versus never OC use because of the high heterogeneity of the studies and the low clinical relevance of the question.

PE Incidence Among OC Users

Most studies included PE in the definition of VTE. Three studies, however, examined the relationship between OC use and the incidence of PE separately from DVT. Two studies looked at the risk among current users. The third looked at the risk among ever versus never users. There were not enough data for a meta-analysis. One good-quality case-control study[264] evaluated the odds of developing PE, DVT, or both PE and DVT among current versus noncurrent OC users. The adjusted odds ratios were similar for all comparisons. For DVT, the odds ratio was 2.05 (95% CI, 1.46 to 2.89); for PE, odds ratio was 1.56 (95% CI, 1.04 to 2.35); and for both DVT and PE, 1.85 (95% CI, 1.38 to 2.48). A fair-quality cohort study[286] that evaluated the risk of PE for current or former OC users demonstrated a trend toward increased risk among current users, but the confidence intervals were not significant, with a risk ratio of 2.2 (95% CI, 0.8 to 5.9). For former OC users, the odds ratio was 0.8 (95% CI, 0.5 to 1.2). A poor-quality cohort study[288] evaluated the risk of PE among ever versus never users and found a risk ratio of 1.56 (95% CI, 1.14 to 2.14) and a similar risk ratio of 1.60 for DVT alone (95% CI, 1.25 to 2.04). Ever users included current and former users of OCs.

Duration of OC Use

Two fair-quality cohort studies[263,292] and four case-control studies (3 good quality and 1 fair)[262,276,296,302] evaluated the relationship between duration of OC use and risk of VTE. Related data from articles considered part of one study grouping[263,276] are represented in both the case-control and cohort categories due to a relationship between the represented patient populations. There were not enough data for a meta-analysis of the risk of VTE among current OC users by duration of use because of the varying time periods of duration of OC use reported in these 5 studies.

In a European case-control study,[302] women using OCs for 6 months or less had an increased odds of VTE compared with longer users (OR, 3.0; 95% CI, 0.6 to 14.8); however, the vast majority of VTEs (97 of 109) occurred in women using OCs for more than a year. In a second European case-control study,[276] current OC users of more than 1 year had 0.5 times the odds of developing VTE compared with users of less than 1 year. In a good-quality case-control study from the United States,[262] the odds of VTE among current versus noncurrent users was 5.43 (95% CI, 2.12 to 13.94) for use less than 1 year. For women using OCs for 1 to 5 years, the odds were similar at 5.73 (95% CI, 2.98 to 10.99) and were lower for those using OCs for greater than 5 years at 3.12 (95% CI, 1.99 to 4.88). In a European cohort study,[263] the rate ratio (RR) of VTE for current users was higher among women who had used for less than 1 year (RR, 4.17; 95% CI, 3.73 to 4.66) than for those who used OCs 1 to 4 years (RR, 2.98; 95% CI, 2.73 to 3.26) or greater than 4 years (RR, 2.76; 95% CI, 2.53 to 3.02). In a fair-quality case-control study from Europe,[296] the odds of VTE was higher among users of all types of OCs during the first 6 months versus 7 months or more of use (OR, 3.8; 95% CI, 1.8 to 9.0).

OC Formulation

Estrogen Dose

Three studies[260,271,276,293] evaluated the relationship between high estrogen (≥50 mcg) and low estrogen (<50 mcg) OCs on the risk of VTE (Table 44). Of these, two were case-control studies representing 1298 cases and 4804 controls and one cohort study representing 7,782,416 person-years. One study was rated good quality and two fair quality.

Table 44. Data for risk of VTE on low-dose versus high-dose estrogen

Study[a]	Formulation	OR or RR	95% CI	Notes
Low-Dose EE vs. Noncurrent Use				
Bloemenkamp, 1995[260]	EE 30 mcg and desogestrel EE 30 mcg and levonorgestrel EE 35 mcg and noresthisterone or lynestrenol	8.7 3.8 3.8	3.9 to 19.3 1.7 to 8.4 1.2 to 12.5	Premenopausal women
Bloemenkamp, 1999[271]	EE 30 mcg and levonorgestrel EE 30 mcg and desogestrel EE 30 mcg and gestodene EE 20 mcg and desogestrel	3.7 4.9 5.2 24.7	1.9 to 7.2 2.5 to 9.4 1.3 to 20.6 2.8 to 213.5	
Lidegaard, 2002[276]	30-40 EE 20 EE	3.4 4.3	2.4 to 7.1 2.8 to 4.2	<1 year vs nonuse (never + former)
Lidegaard, 2011[293]	EE 30-40 mcg and norethisterone EE 30-40 mcg and phasic levonorgestrel EE 30-40 mcg and levonorgestrel EE 30-40 mcg and norgestimate EE 30-40 mcg and desogestrel EE 30-40 mcg and gestodene EE 30-40 mcg and drospirenone EE 30-40 mcg and cyproterone EE 20 mcg and desogestrel EE 20 mcg and gestodene EE 20 mcg and drospirenone	1.57 2.28 2.19 2.56 4.21 4.23 4.47 4.10 3.26 3.50 4.84	0.84 to 2.92 1.85 to 2.83 1.74 to 2.75 2.18 to 3.01 3.63 to 4.87 3.87 to 4.63 3.91 to 5.11 3.37 to 4.99 2.88 to 3.69 3.09 to 3.97 3.19 to 7.33	Adjusted relative risk
High-dose EE vs. Noncurrent Use				
Bloemenkamp, 1995[260]	EE 50 mcg and levonorgestrel or lynestrenol	3.4	1.1 to 10.7	Premenopausal women
Bloemenkamp, 1999[271]	EE 50 mcg and lynestrenol or levonorgestrel or noresthisterone	8.7	2.9 to 25.8	
Lidegaard, 2002[276]	50 EE	4.2	2.4 to 7.1	<1 year vs nonuse (never + former)
Lidegaard, 2011[293]	EE 50 mcg and norethisterone EE 50 mcg and levonorgestrel	5.66 3.54	3.12 to 10.3 2.48 to 5.05	Adjusted relative risk

CI = confidence interval; EE = ethinyl estradiol; OR = odds ratio; RR = relative risk

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

Table 45 lists the odds ratios for the meta-analysis of estrogen dose level. The cohort study[293] was not included in the meta-analysis due to the inability to calculate an odds ratio for the data. The results show no differences in the incidence of VTE by estrogen dose level. A formal test for difference gives a p-value of 0.7974. There was no significant heterogeneity. The estimated value of σ is 0.0.

Table 45. Estimated odds ratio by estrogen-dose level (VTE incidence)

Estrogen Dose	Odds Ratio (95% Confidence Interval)
Low	3.39 (2.32 to 4.96)
High	3.06 (1.32 to 7.10)

However, in the study by Lidegaard et al.,[293] which was not included in this meta-analysis, the first-generation progestin norethisterone in combination with 50 mcg of ethinyl estradiol was associated with a higher risk (RR 5.66; 95% CI, 3.12 to 10.3) than all of the other formulations studied, including norethisterone in combination with 30 to 40 mcg of ethinyl estradiol (RR 1.57; CI, 0.84 to 2.92) and norethisterone without estrogen (RR 0.56; CI, 0.29 to 1.07). These findings suggest that an increase in the ethinyl estradiol dose in combination with norethisterone from 30–40 mcg to 50 mcg may be associated with a more than doubling of risk of VTE. Notably, there was not as large an increase in VTE risk associated with high-dose versus low-dose estrogen in combination with levonorgestrel (RR 3.54 with high-dose and RR 2.19 with low-dose, overlapping confidence intervals).

We were unable to conduct a meta-analysis for the odds of VTE among progestin-only OC users (i.e., pills containing no estrogen); however, several studies addressed this question. A European case-control study[276] found a nonsignificant increase in the odds of VTE (OR 2.0; 95% CI, 0.8 to 5.1) for progestin-only OC users compared with nonusers. This same group of investigators[293] subsequently reported data from a large cohort of women in Denmark that demonstrated a nonsignificant decrease in the relative risk of VTE for progestin-only OC users compared with nonusers (RR for norethisterone 0.56; CI, 0.29 to 1.07 and RR for desogestrel 0.64; CI, 0.29 to 1.42). A multinational case-control study[272] also found no difference in the odds of VTE (OR 0.68; CI, 0.28 to 1.66) among current users of progestin-only OCs versus nonusers.

Progestin Generation

As discussed previously, for the purpose of our analyses, first-generation progestins include norethindrone and ethynodiol diacetate; second-generation include levonorgestrel and norgestrel; third-generation include gestodene, desogestrel, and norgestimate; and fourth-generation include drospirenone, dienogest, and cytoproterone acetate. Six case-control studies representing 4257 cases and 11,791 controls[181,261,270,273,276,280,281,284] were included in this meta-analysis examining the effect on VTE incidence of varying progestin generations in current users of combination OCs.

Four studies were rated good quality and three fair quality. Only one study[280] included patients from the United States. Table 46 lists the included studies, generation of progesterone studied, and odds ratios. An additional large cohort study representing 8,010,290 person-years[293] reported relative risks of VTE associated with several different progestin generations. The findings from this study are summarized in Table 46 but could not be included in the meta-analysis because odds ratios were not reported.

Table 46. Data for outcomes on progestin generation (VTE incidence)

Study[a]	Formulation[b] (Vs. Noncurrent OC Use)	OR	95% CI	Notes
First Generation				
Anonymous, 1995[181]	First generation/ EE < 50 mcg First generation/EE ≥ 50 mcg	3.37 4.05	1.44 to 7.93 1.92 to 8.54	Europe only (developing countries excluded)
Lidegaard, 1998[270]	First generation	1.8	0.9 to 3.6	VTE (PE + DVT)
Lewis, 1999[261]	First generation	8.48	3.03 to 23.86	
Lidegaard, 2002[276]	<1 year of use first generation	4.1	2.4 to 7.1	
Austin, 2009[280]	First generation	4.1	1.1 to 14.9	African-American women
Van Hylckama Vlieg, 2009[281]	Lynestrenol Noresthisterone	5.6 3.9	3.0 to 10.2 1.4 to 10.6	
Lidegaard, 2011[293]	Norethisterone/EE 50 mcg Norethisterone/EE 30-40 mcg Norethisterone (no estrogen)	5.66 1.57 0.56	3.12 to 10.3 0.84 to 2.92 0.29 to 1.07	Adjusted relative risk (not included in meta-analysis of odds ratios)
Second Generation				
Anonymous, 1995[181]	Second generation/EE ≥ 50 mcg Second generation/EE < 50 mcg	3.83 3.61	2.44 to 6.02 2.53 to 5.13	Europe only (developing countries excluded)
Suissa, 1997[273]	Second generation	6.6	2.5 to 17.8	<1 year of use
Lidegaard, 1998[270]	Second generation	1.6	1.0 to 2.5	
Lewis, 1999[261]	Second generation Other second generation Levonorgestrel	2.85 3.25 2.63	1.92 to 4.22 1.89 to 5.58 1.75 to 3.95	
Lidegaard, 2002[276]	Second generation Levonorgestrel	2.9 3.6	2.2 to 3.8 2.6 to 4.9	
Austin, 2009[280]	Second generation	2.9	0.9 to 9.3	African-American women
Van Hylckama Vlieg, 2009[281]	Second generation (levonorgestrel) vs. none	3.6	2.9, 4.6	
Heinemann, 2010[284]	Second generation	3.14	2.21 to 4.47	
Lidegaard, 2011[293]	Levonorgestrel/EE 50 mcg Levonorgestrel/EE 30-40 mcg Phasic levonorgestrel/EE 30-40 mcg	3.54 2.19 2.28	2.48 to 5.05 1.74 to 2.75 1.85 to 2.83	Adjusted relative risk (not included in meta-analysis of odds ratios)
Third Generation				
Anonymous, 1995[181]	Third generation/EE < 50 mcg	7.36	4.20 to 12.90	Europe only (developing countries excluded)
Lewis, 1999[261]	Third generation Norgestimate Desogestrel 30 mcg Gestodene Desogestrel 20 mcg	2.26 3.65 2.52 2.25 1.56	1.46 to 3.50 2.17 to 6.12 1.56 to 4.09 1.40 to 3.60 0.85 to 2.86	
Austin, 2009[280]	Third generation	3.4	0.48 to 20.3	African-American women
Lidegaard, 2011[293]	Norgestimate/EE 30-40 mcg Desogestrel/EE 30-40 mcg Gestodene/EE 30-40 mcg	2.56 4.21 4.23	2.18 to 3.01 3.63 to 4.87 3.87 to 4.63	Adjusted relative risk (not included in meta-analysis of odds ratios)

Table 46. Data for outcomes on progestin generation (VTE incidence) (continued)

Study[a]	Formulation[b] (Vs. Noncurrent OC Use)	OR	95% CI	Notes
Fourth Generation				
Van Hylckama Vlieg, 2009[281]	Drospirenone Cyproterone acetate	6.3 6.8	2.9 to 13.7 4.7 to 10.0	
Lidegaard, 2011[293]	Drospirenone/EE 30-40 mcg Cyproterone/EE 30-40 mcg Drospirenone/EE 20 mcg	4.47 4.10 4.84	3.91 to 5.11 3.37 to 4.99 3.19 to 7.33	Adjusted relative risk (not included in meta-analysis of odds ratios)

CI = confidence interval; EE = ethinyl estradiol; OC = oral contraceptive; OR = odds ratio

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]First-generation progestins = norethindrone and ethynodiol diacetate; second-generation = levonorgestrel and norgestrel; third-generation = gestodene, desogestrel, and norgestimate; fourth-generation = drospirenone, dienogest, and cytoproterone acetate.

Table 47 lists the results of the meta-analysis. We found no difference in the odds of VTE by progestin generation. An overall test for differences gives a chi-square value of 8.1 for 3 degrees of freedom, p=0.044. There was significant heterogeneity. The estimated value of σ is 0.24. The t-value is 4.89 for 11 degrees of freedom, p=0.0005. The value of σ is larger than many of the standard errors for the observed odds ratios.

Table 47. Estimated odds ratio by progestin generation of combined OCs relative to noncurrent use (VTE incidence)

Generation	Odds Ratio (95% Confidence Interval)
First	4.06 (2.66 to 6.19)
Second	3.28 (2,49 to 4.31)
Third	4.06 (3.09 to 5.32)
Fourth	5.36 (2.78 to 10.32)

Additional reports[260,268,271,279,283,287,291,296,297,299-301,311,312] giving information about the risk of VTE associated with different generations of progestin use are provided in Table 48. These data were not in a format that was useful for meta-analysis because the comparisons were between users of various types of OCs, and the studies did not report odds of VTE between current and noncurrent users. There were also many overlapping patients between these studies and between some of these studies and those included in the meta-analysis reported above. One fair-quality cohort study,[287] one good-quality case-control study,[279] and one fair-quality case-control study,[299] all conducted in the United Kingdom, found no difference in the odds or risk of VTE among users of OCs containing progestins of different generations but similar ethinyl estradiol doses. A good quality large European cohort study[297] found no difference in VTE odds among current users of dienogest- or drospirenone-containing OCs and those using other OCs containing similar estrogen dose. Another fair quality case control study[283] had similar findings. Another fair-quality European case-control study[260] found a significant increase in odds of VTE among current users of desogestrel, a third-generation OC, compared with first- and second-generation OCs (OR, 2.5; 95% CI, 1.2 to 5.2). A separate, good-quality case-control study[271] found no difference in VTE risk between OC users of third-generation progestins versus those using second-generation progestins. A large, fair-quality cohort study[291] reported VTE incidence among initiators of OCs containing drospirenone (a fourth-generation OC) versus initiators of

other OCs followed on average for 7.6 months. They found no significant difference in risk (RR, 0.9; 95% CI, 0.5 to 1.6).

On the other hand, a good-quality analysis of the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Conception[268] reported statistically significant increases in the odds of VTE associated with third-generation progestins desogestrel (OR, 2.4; 95% CI, 1.3 to 4.6) and gestodene (OR, 3.1; 95% CI, 1.6 to 5.9) compared with the second-generation progestin levonorgestrel. Jick et al.[296] also reported higher odds of VTE associated with third-generation OCs compared with the second-generation progestin levonorgestrel (OR, 2.3; 95% CI, 1.3 to 3.9) in a good-quality case-control study using the U.K. General Practice Research Database. Herings et al.[301] reported similar findings among a population of Dutch women; in a fair-quality cohort study, they reported a risk ratio of 4.2 (95% CI, 1.7 to 10.2) for VTE among new users of third-generation progestins compared with new users of levonorgestrel. Another fair-quality case-control study conducted in the United States[312] demonstrated an increased odds ratio of VTE associated with the fourth-generation progestin drospirenone compared with levonorgestrel (OR, 2.4; 95% CI, 1.7 to 3.4). Similarly, Parkin et al.[300] reported an increased risk of nonfatal VTE associated with the fourth-generation progestin drospirenone compared with levonorgestrel (OR, 3.3; 95% CI, 1.4 to 7.6) in a fair-quality case-control study that used the U.K. General Practice Research Database. Finally, a fair-quality cohort study conducted in Israel[311] reported an elevated risk ratio for VTE of 1.43 (95% CI, 1.15 to 1.78) associated with OCs that contained drospirenone, relative to OCs that contained a third-generation progestin.

Table 48. Comparative risk of VTE among different progestin formulations and generations (VTE incidence)

Study[a]	Formulation[b]	Referent	OR, RR, or HR	95% CI	Notes
Anonymous, 1995[268]	Desogestrel Gestodene Desogestrel or gestodene	Levonorgestrel Levonorgestrel Levonorgestrel	2.4 3.1 2.7	1.3 to 4.6 1.6 to 5.9 1.6 to 4.6	OR adjusted for BMI, alcohol consumption, Oxford region varicose veins, HTN in pregnancy, smoking
Bloemenkamp, 1995[260]	Desogestrel Desogestrel with 30 mcg EE	Levonorgestrel All other OCs	2.2 2.5	0.9 to 5.4 1.2 to 5.2	RR adjusted for age
Farmer, 1997[287]	All second generation Levonorgestrel Levonorgestrel Levonorgestrel Levonorgestrel Levonorgestrel Monophasic levonorgestrel Monophasic levonorgestrel	All third generation Other second generation Desogestrel/EE 30 mcg Desogestrel/EE 20 mcg All desogestrel Gestodene Sequential levonorgestrel All third generation	1.68 0.51 1.17 2.51 1.76 1.32 2.09 1.97	1.04 to 2.75 0.19 to 1.33 0.60 to 2.26 1.09 to 5.44 0.91 to 3.48 0.70 to 2.49 0.93 to 4.70 1.00 to 3.87	RR adjusted for 5-year bands
Bloemenkamp, 1999[271]	Monophasic third generation	Levonorgestrel	1.9	0.8 to 4.5	OR adjusted for age, family history, center, calendar time
Herings, 1999[301]	Third-generation OC	Second-generation OC	4.2	1.7 to 10.2	RR adjusted for year and age
Todd, 1999[299]	Desogestrel Gestodene Norethisterone Norgestimate Cyproterone acetate	Levonorgestrel Levonorgestrel Levonorgestrel Levonorgestrel Levonorgestrel	1.4 1.3 0.5 0.7 0.8	0.7 to 2.8 0.7 to 2.7 0.2 to 1.6 0.2 to 2.4 0.2 to 3.3	OR adjusted for BMI, smoking, diastolic blood pressure, non-OC prescriptions

Table 48. Comparative risk of VTE among different progestin formulations and generations (VTE incidence) (continued)

Study[a]	Formulation[b]	Referent	OR, RR, or HR	95% CI	Notes
Farmer, 2000[279c]	Desogestrel/EE 30 mcg Gestodene/EE 30 mcg Desogestrel/EE 20 mcg Triphasic levonorgestrel/EE Norgestimate/EE 35 mcg Norethisterone/EE 35 mcg Cyproterone/EE 35 mcg Drospirenone Gestodene Norgestimate	Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel/EE 30 mcg Levonorgestrel Levonorgestrel Levonorgestrel	1.0 0.8 1.3 1.4 0.9 3.3 0.7 0.9 0.7 0.7	0.6 to 1.6 0.5 to 1.3 0.6 to 2.5 0.6 to 0.8 1.6 to 0.4 1.0 to 10 0.3 to 1.4 0.6 to 1.4 0.4 to 1.1 0.3 to 1.4	OR adjusted for BMI, smoking status, diastolic BP, asthma, duration of OC exposure, and non-OC/nonasthma prescriptions OR adjusted by year of birth
Jick, 2000[296]	Third-generation OCs	Levonorgestrel	2.3	1.3 to 3.9	OR adjusted for BMI, smoking, duration of OC use, OC switching. Controls matched by year of birth, index date, general practice
Dinger, 2007[297c]	Desogestrel Desogestrel Desogestrel	Levonorgestrel and other OCs Levonorgestrel Other OCs	1.1 1.0 1.3	0.7 to 1.7 0.6 to 1.7 0.8 to 2.0	HR adjusted for age, BMI, duration of OC use, VTE history
Seeger, 2007[291]	Drospirenone/EE	Other OCs	1.0	0.5 to 1.9	RR Current OC use
Dinger, 2010[283]	Dienogest/EE Dienogest/EE Desogestrel/EE	Other low-dose OC Low-dose levonorgestrel/EE Low-dose levonorgestrel/EE	0.9 1.0 1.0	0.6 to 1.4 0.6 to 1.8 0.5 to 1.8	OR adjusted for history of VTE, BMI, duration of OC use, parity, education, chronic disease, medications, smoking
Gronich, 2011[311]	Drospirenone	Third-generation OC	1.43	1.15 to 1.78	Rate ratio adjusted for age, diabetes, hyperlipidemia, hypertension, cancer, smoking, obesity, duration of use

Table 48. Comparative risk of VTE among different progestin formulations and generations (VTE incidence) (continued)

Study[a]	Formulation[b]	Referent	OR, RR, or HR	95% CI	Notes
Jick, 2011[312]	Drospirenone	Levonorgestrel	2.4	1.7 to 3.4	OR adjusted for age, index year, and duration of OC use
Parkin, 2011[300]	Drospirenone	Levonorgestrel	3.3	1.4 to 7.6	OR adjusted for BMI, using multiple imputation analysis

BMI = body mass index; CI = confidence interval; EE = ethinyl estradiol; HR = hazard ratio; OC = oral contraceptive; OR = odds ratio; RR = risk ratio; VTE = venous thromboembolism

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]First-generation progestins=norethindrone and ethynodiol diacetate; second-generation=levonorgestrel and norgestrel; third-generation=gestodene, desogestrel, and norgestimate; fourth-generation=drospirenone, dienogest, and cytoproterone acetate.

[c]Published study reported odds ratios and 95% CIs with levonorgestrel as the index value. For consistency in this table, we reversed the direction of this comparison and converted the odds ratios and 95% CIs to reflect the relative odds of VTE with use of levonorgestrel as the reference group.

Special Populations and Risk of VTE with OC use

Blood-Clotting Disorders

Several studies evaluated the risk of VTE among special populations, including women with known predispositions to blood clotting. We were not able to perform a meta-analysis on this relationship because of a small number of studies that differed from each other in several important ways, including patient population and selections of controls.

One fair-quality case-control study[269] found an interaction between the use of OCs and the presence of inherited thrombophilia—protein C, protein S, antithrombin deficiencies, or Factor V Leiden mutation—such that OC users with inherited thrombophilia had a higher risk of VTE than is explained by the presence of either risk factor (i.e., a "multiplicative" effect). The odds ratio for inherited thrombophilia was 2.6 (95% CI, 0.7 to 9.3), and the odds ratio for inherited thrombophilia plus OC use was 63 (CI, 6.2 to 65). A second, poor-quality case-control study[275] found that Factor V Leiden carriers compared with noncarriers had an odds ratio of 1.7 (CI, 0.6 to 4.8), while carriers plus OC users had an odds ratio of 6.4 (CI, 2.8 to 14.3). Another fair-quality case-control study[280] showed a similar finding for a population of OC users with and without sickle cell trait. Compared with a reference group of nonusers without sickle cell trait, OC users without sickle cell trait had an odds ratio for VTE of 2.6 (CI, 1.1 to 6.2) and nonusers with sickle cell trait had an odds ratio of 1.8 (CI, 0.51 to 6.3). However, sickle cell trait patients who also used OCs had an odds ratio of 12.1 (CI, 2.8 to 52) for VTE. The sample size was too small to allow correction for potential confounding variables. Two cohorts of women whose family members had been diagnosed with VTE[292,295] had a two-fold increased risk of VTE during current OC use and risk regardless of presence of known thrombophilias.

OC Use and Venous Thromboembolism Mortality

No studies evaluated the association between OC use and mortality from VTE events.

Strength of Evidence for OC Use and Risk of Venous Thromboembolism

We found strong evidence that current OC use conferred a three-fold increased risk of VTE and PE when compared with the risk among noncurrent users (Table 49). The risk of VTE did not change among users of pills containing varying estrogen doses or progestin generations.

Table 49. Strength of evidence domains for the effect of OC use on venous thromboembolic events

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of All VTE and Mixed DVT/PE						
Current vs. noncurrent use/never	14 (15,466 plus 9,906,890 person-years)	Medium	Consistent	Direct	Precise	**High** 2.97 (2.46 to 3.59)
Incidence of PE Only						
Current vs. noncurrent use/never	3 (863 plus 2,124,474 person-years)	Medium	Consistent	Direct	Precise	**Low** Elevated risk appears similar to that of VTE
Incidence of All VTE and Mixed DVT/PE						
Duration of use	5 (6955 plus 7,782,416 person-years)	Medium	Consistent	Direct	Precise	**Low** Elevated risk may be present during first year of use
Estrogen	3 (6102 plus 7,782,416 person-years)	Medium	Consistent	Direct	Precise	**High** Low dose: 3.39 (2.32 to 4.96) High dose: 3.06 (1.32 to 7.10)
Progestin	6 (16,048)	Medium	Consistent	Direct	Precise	**High** First generation: 4.06 (2.66 to 6.19) Second generation: 3.28 (2.49 to 4.31) Third generation: 4.06 (3.09 to 5.32) Fourth generation: 5.36 (2.78 to 10.32)
Mortality From VTE						
Current vs. noncurrent use/never	0	NA	NA	NA	NA	**Insufficient** NA

CI = confidence interval; DVT = deep venous thrombosis; PE = pulmonary embolism; SOE = strength of evidence; VTE = venous thromboembolism

OC Use and Stroke Incidence

We identified 15 studies that evaluated the association between OC use and the incidence of stroke, including ischemic, hemorrhagic, and undifferentiated stroke.[261,265,267,272,288,304-307,314-333] Of these, 10 were case-control studies, 4 were cohort studies, and 1 was a pooled analysis; 5 studies were rated good quality, 9 fair quality, and 3 poor quality (Table 50). The pooled analysis[332] includes data from the individual studies by Petitti et al.[315] and Schwartz et al.[333] Nine

studies assembled cohorts that were either fully or partially based in Europe or the United Kingdom; three studies occurred in the United States. All 10 case-control studies recruited or identified patients from hospitals or hospital databases.

Table 50. Study characteristics and association between OC use and stroke incidence

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
			Case-Control				
Tzourio,1995[314]	**Patients <45 yr in 5 hospitals in Paris** Cases: 72 ischemic stroke, hospital Controls: 173 no stroke, hospital Recruitment period: 1990–1993 Type of stroke: Ischemic	NA	NA	NA	France	Fair	3
Petitti,1996[315]	**Members of California Kaiser Permanente Medical Care Program aged 15–44 yr** *Ischemic stroke* Cases: 144 ischemic stroke, hospital and administrative records Controls: 744, hospital and administrative records *Hemorrhagic stroke* Cases: 151 hemorrhagic stroke, hospital and administrative records Controls: 744 hospital and administrative records Recruitment period: 1991–1994	1.18 1.14	0.54 to 2.59 0.60 to 1.16	Race, BMI, smoking, treated diabetes and hypertension	U.S.	Fair	1 2
Anonymous, 1996[317] Anonymous, 1996[318] Anonymous, 1998[267] Chang, 1999[316]	**Women aged 20–44 yr in WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone** Contraception Cases: Hospital* Controls: No stroke, hospital* *Different sample size across articles Recruitment period: 1990–1994	4.20[316] (ischemic stroke) 1.10[316] (hemor-rhagic stroke)	1.74 to 10.12 0.63 to 1.93	Smoking, history of hypertension	UK, Germany, Hungary, Yugoslavia, Slovenia	Good	1 2

Table 50. Study characteristics and association between OC use and stroke incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Heinemann, 1997[326] Heinemann, 1999[272] Lewis, 1999[261]	**Women aged 16–44 yr in Transnational Study on Oral Contraceptives and the Health of Young Women** Cases: Undifferentiated stroke, hospital* Controls: No MI, thromboembolic CVA, or VTE, hospital and community* *Different sample size across articles Recruitment period: 1993–1996	2.86[261]	2.02 to 4.04	Hypertension, occupation, education level, hyperlipidemia, genetic polymorphisms of ACE gene	Austria, France, Germany, Switzerland, UK	Fair	1
Schwartz, 1997[333]	**Members of California Kaiser Permanente Medical Care Program aged 15–44 yr** ***Ischemic stroke*** Cases: 60 ischemic stroke, hospital and administrative records Controls: 485, community *Hemorrhagic stroke* Cases: 102 hemorrhagic stroke, hospital and administrative records Controls: 485 community Recruitment period: 1991–1994	0.90 0.93	0.27 to 2.94 0.37 to 2.31	Age, treated hypertension, smoking, race, alcohol use	U.S.	Good	1 2
Barinagarrementeria, 1998[327]	**Women aged 11–44 yr in stroke clinic and neurology department of a hospital in Mexico City** Cases: 130 undifferentiated stroke, hospital Controls: 122 no stroke, hospital Recruitment period: "Last 11 years"	2.5	0.8 to 8.1	Unadjusted	Mexico	Poor	1
Kemmeren, 2002[320]	**Women aged 19–49 yr in Risk of Arterial Thrombosis in Relation to Oral Contraceptives Study** Cases: 203 ischemic stroke, hospital Controls: 925, community Recruitment period: 1990–1995	2.1	1.5 to 3.1	Age, area of residence, calendar yr	Netherlands	Good	3

Table 50. Study characteristics and association between OC use and stroke incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued) (continued)							
Siritho, 2003[322]	**Patients aged 15–55 yr in 4 city hospitals in Melbourne** Cases: 234 ischemic stroke, hospital discharge records Controls: 234, community Recruitment period: 1984–1996	1.62	0.69 to 3.83	Smoking, alcohol, exercise, cholesterol, MI, hypertension, TIA, diabetes	Australia	Fair	1
Martinelli, 2006[323]	**Woman <45 yr referred to a thrombosis center** Cases: 105, ischemic stroke, hospital Controls: 293, healthy, partner or friend of cases	NA	NA	NA	Italy	Poor	4
Wang, 2012[325] Li, 2010[324]	**25 towns in Jiangsu Province** *Either ischemic or hemorrhagic stroke* Cases: 449 either ischemic or hemorrhagic stroke, hospital Controls: 830 no stroke, hospital	4.05	2.19 to 7.47	Parity, BMI, smoking, hypertension, hyperlipidemia, alcohol use, diabetes, family history of stroke, duration of current OC use	China	Fair	1
Cohort							
Hannaford, 1998[288]	**Royal College of General Practitioner's Oral Contraception study** Exposed: 335,181 person-years Unexposed: 28,727 person-years Mean age at study entry: 49 Recruitment period: 1968–NR	NA	NA	NA	UK	Poor	3
Mant, 1998[265]	**Women aged 25–39 yr in Oxford Family Planning Association Study** Exposed: 186,848 person-years Unexposed: 123,716 person-years Note: After age 45, only women who had never used OCs or those who had used it for ≥8 yr were followed until 1994. Recruitment period: 1968–1974	2.9	1.3 to 6.7	Age, parity, BMI, smoking, social class	UK	Fair	1

Table 50. Study characteristics and association between OC use and stroke incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort (continued)							
Yang, 2009[319]	**Women aged 30–49 yr in Women's Lifestyle and Health Cohort Study** Exposed: 38,258 Unexposed: 7471 Recruitment period: 1991–1992	1.1 0.4	0.6 to 2.0 0.1 to 2.1	Age, BMI, smoking, education, physical activity, alcohol use, high blood pressure, diabetes	Sweden	Fair	1 2
Lidegaard, 2012[329]	**Women aged 15–49 yr in Denmark** *Either ischemic or undifferentiated stroke* Exposed: 4,651,766 person-years Unexposed: 9,336,662 person-years *Ischemic stroke* Exposed: 4,651,766 person-years Unexposed: 9,336,662 person-years Recruitment period: 1995–2009	NR	NR NR	Age, education, year, risk factors	Denmark	Fair	5

Table 50. Study characteristics and association between OC use and stroke incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
			Pooled				
Schwartz, 1998[332]	**Members of California Kaiser Permanente Medical Care Program and Washington State aged 18–44 yr** *Ischemic stroke* Cases: 175 ischemic stroke, hospital and administrative records Controls: 485, hospital and administrative records and community *Hemorrhagic stroke* Cases: 198 hemorrhagic stroke, hospital and administrative records Controls: 485 hospital and administrative records and community Recruitment period: 1991–1994	NR	NR	NA	U.S.	Good	6

BMI = body mass index; CI = confidence interval; mo = month/months; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; U.S. = United States; VTE = venous thromboembolism; WHO = World Health Organization; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Meta-analysis code: 1=Included in ischemic stroke meta-analysis; 2=Included in hemorrhagic stroke meta-analysis; 3=Excluded due to current versus noncurrent OC use odds ratio not reported; 4=Excluded due to population of high-risk patients recruited from a thrombosis center; 5=Excluded due to adjusted relative risks as calculated from person-years of exposure cannot be converted to odds ratios; 6=Excluded this pooled study due to having duplicate patients reported in single studies above.

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Current Versus Noncurrent OC Use

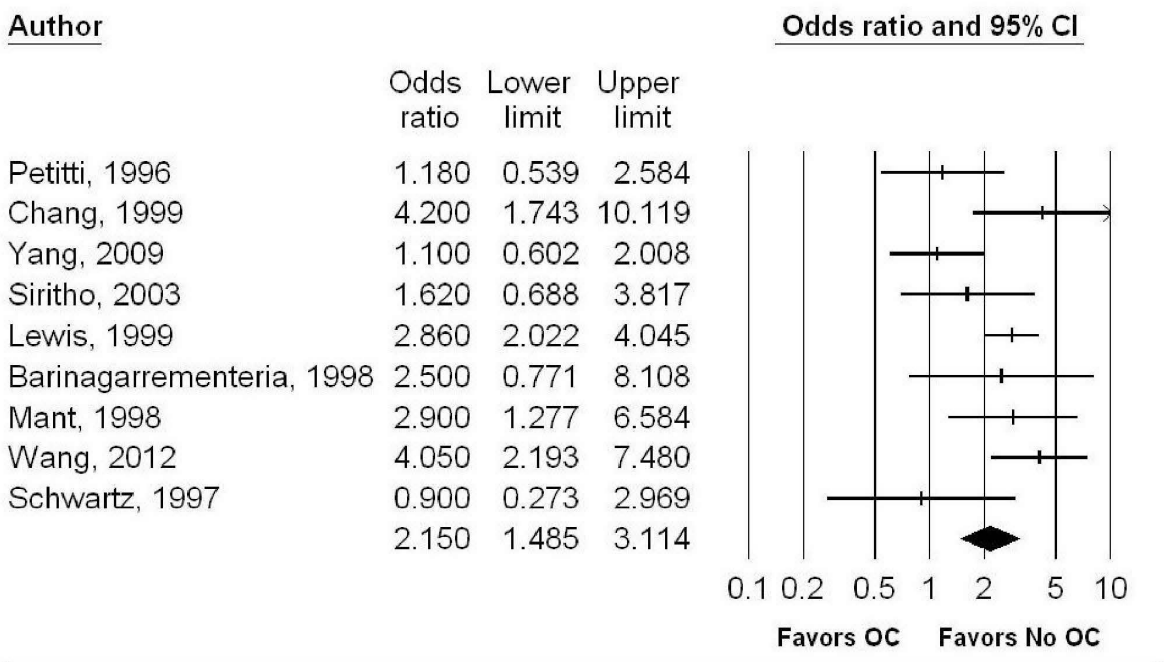
Of the 15 studies that evaluated the association between OC use and the incidence of stroke, nine[261,265,315,316,319,322,325,327,333] were included in a meta-analysis examining the effect of current versus noncurrent OC use on ischemic or undifferentiated stroke incidence. Of these, 7 were case-control studies representing 1490 cases and 3786 controls, and 2 were cohort studies representing 45,729 participants and 310,564 person-years. Two studies were rated good quality, six studies were rated fair quality, and one poor quality (Table 50). One study[327] did not specify whether the patients included in the analysis had ischemic or hemorrhagic stroke; we assumed that the majority of strokes were ischemic, and therefore we included this study in the meta-analysis. Abstracted data not included in this meta-analysis is specified (with rationale) in Table 50. Reasons for exclusion from this analysis included the following: no reporting of an odds ratio for current versus noncurrent use of OCs; representing a special, high-risk population; and reporting results not as odds ratios, but as relative risks calculated from person-years of exposure.

We also conducted separate meta-analyses of the seven studies of known ischemic stroke[261,265,315,316,319,322,333] representing 911 cases, 2834 controls, 38,258 exposed people, 7471 unexposed people, 186,848 person-years of exposure, and 123,716 unexposed person-years. We conducted a separate meta-analysis of the four studies that reported data separately for known hemorrhagic stroke representing 688 cases, 1965 controls, 38,258 exposed people, and 7471 unexposed people.[315,316,319,333]

Ischemic/Undifferentiated Stroke

We included all ischemic study results and also included any study of undifferentiated stroke if the ischemic stroke results were not available. Figure 34 shows that the random effects estimated odds ratio is 2.15 (95% CI, 1.49 to 3.11), demonstrating a significant increase in stroke risk for current OC use. There was significant heterogeneity, with a Q-value of 818.47 for 8 degrees of freedom, p=0.018.

Figure 34. Forest plot for ischemic/undifferentiated stroke



CI = confidence interval; OC = oral contraceptive

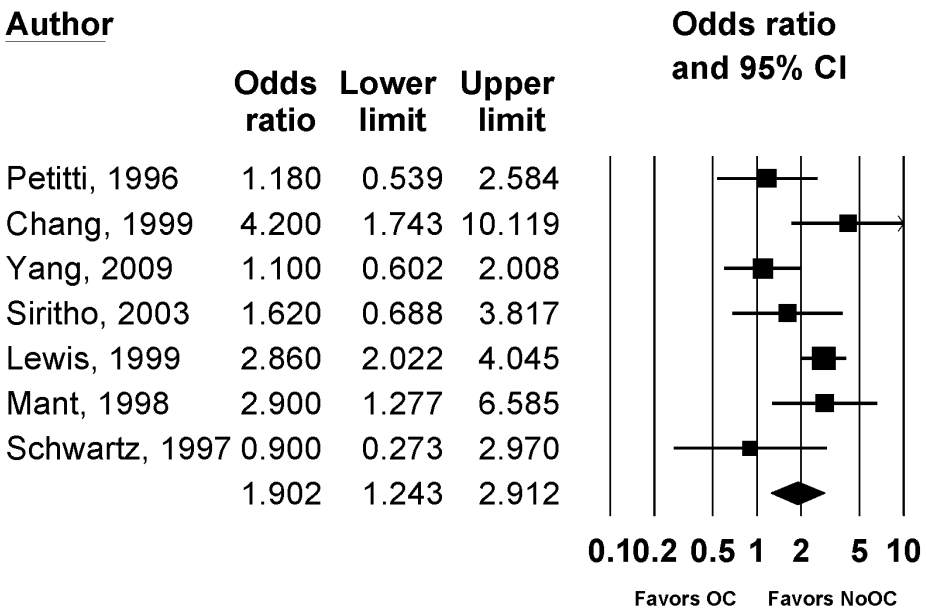
Sensitivity Analyses

We performed a sensitivity analysis by dropping the single poor-quality study.[327] The results were essentially unchanged with an odds ratio of 2.12 (95% CI, 1.42 to 3.16). Only two of the studies in this meta-analysis[315,333] were conducted in the United States; we did not, therefore, conduct a sensitivity analysis by excluding studies that did not include patients in the United States.

Ischemic Stroke

Figure 35 shows the odds ratios for the five case-control and two cohort studies of ischemic stroke incidence as a function of OC use. These studies represent a total of 1,100 cases, 2,975 controls, 38,258 exposed people, 7471 unexposed people, 186,848 person-years of exposure, and 123,716 unexposed person-years. The random-effects estimated odds ratio is 1.90 (95% CI, 1.24 to 2.91). There was significant heterogeneity, with a Q-value of 5.76 for 6 degrees of freedom, p=0.036.

Figure 35. Forest plot for ischemic stroke

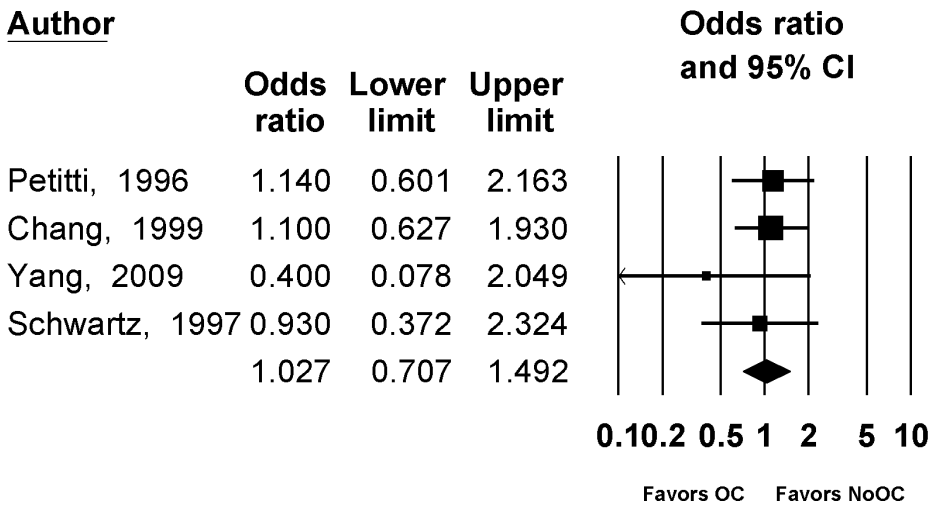


CI = confidence interval; OC = oral contraceptive

Hemorrhagic Stroke

Figure 36 shows the odds ratios for the three case-control studies and one cohort study of hemorrhagic stroke incidence as a function of OC use. The random-effects estimated odds ratio is 1.03 (95% CI, 0.71 to 1.49), showing no evidence of increased hemorrhagic stroke risk among current OC users. There was no significant heterogeneity, with a Q-value of 1.48 for 3 degrees of freedom, p=0.489. Although current OC use is associated with a doubling of risk for ischemic/undifferentiated stroke, current OC use does not appear to be associated with an increased risk of hemorrhagic stroke.

Figure 36. Forest plot for hemorrhagic stroke



CI = confidence interval; OC = oral contraceptive

Past OC Use and Stroke Incidence

The majority of studies evaluated the risk of stroke among current users compared with noncurrent users; however, three studies evaluated whether there was any risk associated with ever versus never use of OCs. One poor-quality cohort study[288] found an elevated risk for cerebrovascular disease associated with ever OC use compared with never use (RR 1.37; 95% CI, 1.12 to 1.67). OC users in this study included current users. One Australian case-control study[322] found a trend toward increased odds of ischemic stroke among current OC users but no evidence of increased odds among past users. A case-control study from China[324,325] found a mildly increased risk of stroke among past users (OR 1.36; CI,1.04 to 1.77) but a much greater increased risk of stroke among current users (OR 4.05; CI,2.19 to 7.47). A fair-quality cohort study[319] found no elevated risk of stroke among current OC users (RR 1.1; CI, 0.6 to 2.0) or past users (RR 0.9; CI, 0.6 to 1.4). In a second fair-quality cohort study,[265] the significant increased risk of ischemic stroke among current users of OCs disappeared among past users (RR 0.7; CI, 0.2 to 2.2).

Duration of OC Use

There was an insufficient number of studies to conduct a meta-analysis examining the effect of duration of OC use on risk of stroke. A fair-quality European cohort study[319] demonstrated no increased risk of stroke with ever OC use; this did not change when stratified by duration of use by less than 5 years, 5 to 10 years, or more than 10 years. A fair-quality U.K. cohort study[265] found no significant difference in stroke risk for ever users who used OCs less than 5 years, 5 to 10 years, 10 to 15 years, 15 to 20 years, or greater than 20 years. A fair-quality Australian case-control study[322] similarly found no significant increased stroke risk by duration of use (up to 8 years or more than 8 years). In a European case-control study,[321] there were similar odds of cerebral thrombosis of any type among current users compared with never users when stratified by duration of use (<1 year, 1–5 years, and >5 years). In a fair-quality nested case-control study from China,[325] ever users of OCs for 15 years or more had increased odds of hemorrhagic stroke

(OR 3.7; CI, 1.9 to 7.3) but not ischemic stroke (OR 1.3; CI, 0.8 to 2.2) when compared with never users.

OC Formulation

Estrogen Dose

Two good-quality and one fair-quality case-control studies[317,320,321] representing 1897 cases and 8080 controls were included in a meta-analysis to evaluate the relationship between high-dose and low-dose estrogen on the risk of ischemic or undifferentiated stroke. Additional data abstracted from a cohort study[329] representing 13,988,428 person-years, and a case-control study involving women without migraines are summarized in Tzourio et al.[314] (Table 51) were not included in the meta-analysis because the former reported relative risks that could not be readily converted to odds ratios, and the latter did not provide confidence intervals. None of these studies included women from the United States.

Table 51. Stroke incidence odds by estrogen dose compared with nonuse of OCs

Study[a]	Comparison[b]	OR	95% CI	Comparison[b]	OR	95% CI	Notes
	Low-Dose vs. Nonuse			High-Dose vs. Nonuse			
Tzourio, 1995[314]	Low (20) Low (30-40)	1.7 2.7	NA NA	High (50)	4.8	NA	Women without migraines; undifferentiated stroke
Anonymous, 1996[317]	Low (<50)	1.27	0.70 to 2.32	High (≥50)	1.42	0.67 to 2.97	Undifferentiated stroke
Kemmeren, 2002[320]	Low (<50)	2.3	1.5 to 3.4	High (50)	3.1	1.2 to 7.9	Undifferentiated stroke
Lidegaard, 2002[321]	Low (20) Low (30-40)	1.7 1.6	1.0 to 3.1 1.3 to 2.0	High (50)	4.5	2.6 to 7.7	Current vs. never use; undifferentiated stroke
Lidegaard, 2012[329]	Norethindrone/ EE 30-40 Levonorgestrel/ EE 30-40 Norgestimate/ EE 30-40 Desogestrel/EE 30-40 Gestodene/EE 30-40 Drospirenone/ EE 30-40 Cyproterone/EE 30-40 Desogestrel/EE 20 Gestodene/EE 20 Drospirenone/ EE 20	2.17 1.65 1.52 2.20 1.80 1.64 1.40 1.53 1.70 0.88	1.49 to 3.15 1.39 to 1.95 1.21 to 1.91 1.79 to 2.69 1.58 to 2.04 1.24 to 2.18 0.97 to 2.03 1.26 to 1.87 1.37 to 2.12 0.22 to 3.53	Norethindrone/ EE 50 Levonorgestrel/ EE 50	1.27 2.26	0.66 to 2.45 1.59 to 3.20	Adjusted relative risk, based on person-years of exposure

CI = confidence interval; EE = ethinyl estradiol; OR = odds ratio

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]First-generation progestins=norethindrone and ethynodiol diacetate; second-generation=levonorgestrel and norgestrel; third-generation=gestodene, desogestrel, and norgestimate; fourth-generation=drospirenone, dienogest, and cyproterone acetate.

Table 52 lists the odds ratios for the meta-analysis of the risk of ischemic/undifferentiated stroke by estrogen dose level. The results show a significant difference by dose. The estimated odds ratio comparing high dose with low dose is 2.37 (95% CI, 1.05 to 5.38, p-value for no difference=0.0437). There was no significant heterogeneity. The estimated value of σ is 0.0.

Table 52. Estimated odds ratios by estrogen dose compared with nonuse of OCs (stroke incidence)

Estrogen Dose	Odds Ratio (95% Confidence Interval)
Low	1.73 (1.29 to 2.32)
High	4.10 (1.91 to 8.80)

The findings from the large cohort study by Lidegaard, et al. provide additional evidence that estrogen dose may affect risk of stroke associated with OC use. This may be modified by the type of progestin the estrogen is combined with. Compared with nonusers of OCs, users of high-dose estrogen with norethindrone had a relative risk for stroke of 1.27 (95% CI, 0.66 to 2.45) compared with a relative risk of 2.17 (95% CI, 1.49 to 3.15) for low-dose estrogen and norethindrone. Interestingly, high-dose estrogen in combination with levonorgestrel was associated with a relative risk for stroke of 2.26 (95% CI, 1.59 to 3.20) compared with a relative risk of 1.65 (95% CI, 1.39 to 1.95) when low-dose estrogen was combined with levonorgestrel.

Two studies investigated the use of progestin-only OCs. A fair-quality U.K. case-control study[272] found no significant increased risk of stroke among current OC users versus nonusers; however, the confidence intervals were very wide (RR, 1.60; 95% CI, 0.24 to 10.72). A good-quality, multinational case-control study[267] found no increased risk of stroke among current versus noncurrent progestin-only OC users (OR, 1.07; 95% CI, 0.62 to 1.86).

Progestin Generation

There was an insufficient number of studies to do a meta-analysis regarding the risk of stroke according to OC use of varying progestin generation. In a fair-quality European case-control study,[321] there was a significantly increased risk for cerebral thrombus among current users of first-generation progestins (OR, 1.8; 95% CI, 1.0 to 3.3) compared with the reference group of second-generation OC users. There was also a slightly decreased risk for third-generation progestin users (OR, 0.6; 95% CI, 0.4 to 0.9) compared with second-generation users. In another good-quality European case-control study,[320] the increased odds of ischemic stroke among current users of contraceptives remained similar when stratified by first-, second- or third-generation OC users. A fair-quality U.K. case-control study[326] also found no significant difference in stroke risk between first-, second-, and third-generation OC users. In a recently published, fair-quality cohort study in which 1,626,158 women contributed 14,251,063 person-years of observation, Lidegaard et al.[329] reported relative risks of thrombotic stroke associated with several different OC formulations compared with nonusers. Relative risks were reported for OCs representing all four progestin generations. No clear pattern emerged regarding potentially different risks of stroke by progestin generation.

Special Populations

Several populations of women are known to be at increased risk for stroke, including women with migraines, thrombophilias, cardiovascular risk factors, and women of older age. We did not identify enough studies to conduct meta-analyses to determine if these risk factors modified the

risk of stroke in OC users. Several studies, however, did provide preliminary information about stroke risk in these populations.

Migraines

Two studies evaluated the risk of stroke among women with migraines who also used OCs. A fair-quality European case-control study[314] found the odds of stroke for OC users with migraines to be 13.9 times that of nonusers without migraines. However, this odds ratio statistically was not significantly different from the four-fold increase in odds reported for both women with migraines only and women who used OCs only. A fair-quality European case-control study[316] found the use of OCs had greater than multiplicative effects on the odds ratios for ischemic stroke among users with migraines (17-fold odds compared with 3-fold for OC users without migraine and 2-fold for women not using OCs who had migraines). This difference was not statistically significant.

Blood-Clotting Disorders

One poor-quality European case-control study[323] found a two-fold increase in odds of stroke in women with a Factor V Leiden mutation; this risk was significantly increased to 13-fold among current OC users with Factor V Leiden. A similar finding was obtained for women with hyperhomocysteinemia (two-fold odds increased to six-fold odds). It is unclear whether these differences were statistically significant. There was no increased risk among women with prothrombin gene mutation whether or not they were users of OCs. One study[324,325] found that women with specific genetic polymorphisms such as ACE I/D, rs10958409GA/AA and rs1333040CT/TT had a greater than multiplicative odds of stroke.

Age

One good-quality European case-control study[320] found the risk of first ischemic stroke among OC users that increased by age. The odds of stroke was 1.3 (95% CI, 0.5 to 3.3) for women 18 to 29 years of age; 2.3 (CI, 1.2 to 4.3) for women 30 to 39 years; and 2.6 (CI, 1.6 to 4.2) for women 40 to 49 years. There was no statistical test of the difference reported.

OC Use and Stroke Mortality

We identified two fair-quality studies and one poor-quality study that evaluated the association between ever versus never OC use and stroke mortality[33,164-166,334] (Table 53).

Table 53. Study characteristics and association between OC use and stroke mortality

Study	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[a]
Case-Control							
Hannaford, 2010[33]	Royal College of General Practitioner's Oral Contraception study Exposed: 28,806 Unexposed: 17,306 Mean age at study entry: 29 (SD 6.6) Recruitment period: 1968–NR	NR	NR	NA	UK	Fair	1
Vessey, 2010[165]	Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study 602,700 person-years (total for exposed and unexposed) Recruitment period: 1968–1974	NR	NR	NA	UK	Fair	1
Gallagher, 2011[334]	Female workers in 526 textile factories in Shanghai Exposed: 366,890 person-years Unexposed: 2,122,083 person-years Recruitment period: 1989–2000	0.65	0.46 to 0.91	Age	China	Poor	1

CI = confidence interval; NA = not applicable; NR = not reported; OR = odds ratio; SD = standard deviation; UK = United Kingdom; yr = year/years

[a]Meta-analysis code: 1 = Included in meta-analysis.

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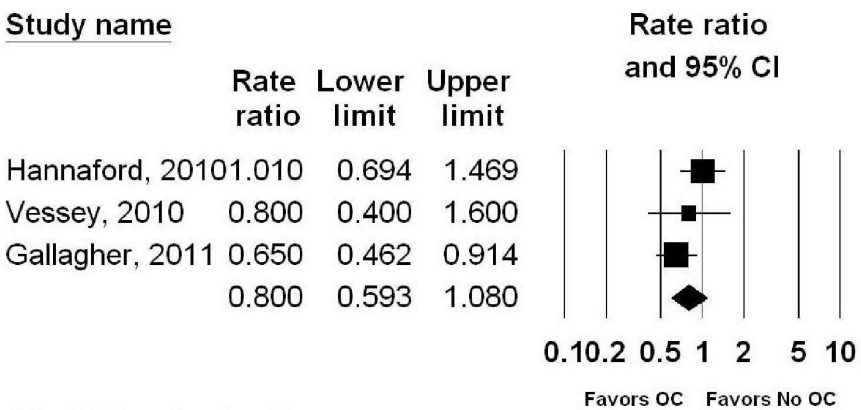
The results of a meta-analysis of these three studies of stroke mortality as a function of OC use are shown in Figure 37. The random-effects estimated odds ratio is 0.80 (95% CI, 0.59 to 1.08). There was no evidence of heterogeneity, with a Q-value of 2.91 for 2 degrees of freedom, p=0.234.

Figure 37. Effect of OC use on stroke mortality



CI = confidence interval; OC = oral contraceptive

Vessey et al.[165] reported the risk of ischemic stroke mortality in ever users by duration of OC use and by time since last use. The risk ratios of mortality from hemorrhagic stroke compared with never OC use were 0.7 (95% CI, 0.4 to 1.3) for less than 4 years of total use; 1.4 (CI, 0.6 to 3.1) for 4 to 8 years of use; and 0.5 (CI, 0.2 to 1.2) for more than 8 years of use. In a second cohort study, calculating the risk of stroke mortality for ever users of OCs, the risk ratio was 1.1 (CI, 0.0 to 6.6) for those who had used within the last 4 years or at the time of death; 0.6 (CI, 0.0 to 3.6) for those who last used between 4 to 12 years prior to death; 0.7 (CI, 0.1 to 2.2) for those who last used 12 to 20 years prior to death; and 0.9 (CI, 0.4 to 1.8) for those who last used more than 20 years prior to death. Similar findings were noted for hemorrhagic stroke.[334]

Strength of Evidence for OC Use and Risk of Stroke

Table 54 shows the strength of evidence for the effects of OC use on the risk of stroke.

Table 54. Strength of evidence domains for the effect of OC use on stroke

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ischemic/Undifferentiated Stroke						
Current vs. noncurrent use/never	9 (54,767 plus 310,564 person-years)	Medium	Consistent	Direct	Precise	**High** 2.15 (1.49 to 3.11)
Duration	4 (51,038 plus 310,626 person-years)	Medium	Consistent	Direct	Imprecise	**Insufficient** NR (Insufficient evidence to support quantitative synthesis of findings)
Estrogen	3 (9977)	Medium	Consistent	Direct	Precise	**High** Low dose: 1.73 (1.29 to 2.32) High dose: 4.10 (1.91 to 8.80)
Progestin	3 (6994)	Medium	Inconsistent	Direct	Imprecise	**Insufficient** NR (heterogeneity in evidence about specific progestin generation)
Incidence of Ischemic Stroke						
Current vs. noncurrent use/never	7 (49,803 plus 310,564 person-years)	Medium	Consistent	Direct	Precise	**High** 1.90 (1.24 to 2.91)
Incidence of Hemorrhagic Stroke						
Current vs. noncurrent use/never	4 (48,382)	Medium	Inconsistent	Direct	Imprecise	**Low** No difference, 1.03 (0.71 to 1.49)
Mortality From Stroke						
Current vs. noncurrent use/never	3 (46,112 plus 3,091,673 person-years)	Medium	Consistent	Direct	Imprecise	**Moderate** 0.80 (0.59 to 1.08)

CI = confidence interval; SOE = strength of evidence

OC Use and Myocardial Infarction Incidence

We identified 11 studies that evaluated the association between OC use and the incidence of myocardial infarction.[261,265,267,270,272,288,304-307,309,313,321,329,331,335-342] Of these, 7 were case-control studies, 4 cohort studies, and 1 pooled analysis of two case-control studies that include data presented in one of the individually included case-control reports. Note that evidence from Lidegaard et al. was abstracted from several publications and included both case-control[270] and cohort[329] study designs. Six studies were rated good quality, 4 fair quality, and 1 poor quality (Table 55). Eight studies (73%) were conducted either fully or partially in Europe or the United Kingdom. Three studies (27%) were conducted in the United States. In the seven case-control

studies, cases were recruited from hospitals or identified by hospital databases. Of these, two studies recruited controls from hospitals, two studies from either hospitals or other settings, and two studies from outpatient-only or community settings. The recruitment source for controls was not clearly indicated in one study.

Table 55. Study characteristics and association between OC use and myocardial infarction incidence

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control							
Anonymous, 1997[337] Anonymous, 1998[267]	**Women aged 20–44 yr in WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception** Cases: 267 acute MI, hospital Controls: 822 patients hospitalized for reasons other than MI Recruitment period: 1989–1995	5.64	2.49 to 12.80	History of hypertension, diabetes, BMI, abnormal blood lipids, smoking status	Africa, Asia, Europe, Latin America	Good	1
Lidegaard, 1998[270]	**Patients aged 15–44 yr from all Danish hospitals** Cases: 94 acute MI, hospital Controls: 1041, source NR Recruitment period: 1994–1995	NR	NR	NA	Denmark	Fair	2
Dunn, 1999[339] Dunn, 1999[338]	**Women aged 16–44 yr in MICA study** Cases: 448 incident MI, hospital Controls: 1728 no MI, outpatient Recruitment period:1993–1995	0.79	0.54 to 1.16	Crude	Denmark	Good	1
Lewis, 1999[261] Heinemann, 1999[272]	**Transnational Study on Oral Contraceptives and the Health of Young Women aged 16–44 yr** Cases: 182 MI, hospital Controls: 635 no MI or thromboembolic CVA, hospital and community Recruitment period: 1993–1996	0.94	0.31 to 2.91	Smoking, hypertension, diabetes, education	Austria, France, Germany, Switzerland, UK	Fair	1

Table 55. Study characteristics and association between OC use and myocardial infarction incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Rosenberg, 2001[340]	**Hospitalized patients <45 yr** Cases: 627 MI, hospital Controls: 2947 no MI, hospital Recruitment period: 1985–1999	1.3	0.8 to 2.2	Age, menopausal status, family history, smoking, region, interview yr, type of interview, hypertension, diabetes mellitus, history of elevated serum cholesterol	U.S.	Good	1
Tanis, 2001[341]	**Women aged 18–49 in Risk of Arterial Thrombosis in Relation to Oral Contraception study** Cases: 248 MI, hospital databases Controls: 925 no history of coronary, cerebral, or peripheral artery disease, community Recruitment period: 1990–1995	2.0	1.5 to 2.8	Age, area of residence and calendar yr	Netherlands	Good	1

Table 55. Study characteristics and association between OC use and myocardial infarction incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
			Cohort				
Hannaford, 1998[288]	**Royal College of General Practitioner's Oral Contraception study** Exposed: 335,181 person-years Unexposed: 228,727 person-years Mean age at study entry: 49 Recruitment period: 1968–NR	NR	NR	NA	UK	Poor	2
Mant, 1998[265]	**Women aged 25–39 in Oxford Family Planning Association Study** Exposed: 186,910 person-years Unexposed: 123,716 person-years Recruitment period: 1968–1974	1.5	0.6 to 3.2	Age, parity, BMI, smoking, social class	UK	Fair	1
Margolis, 2007[342]	**Women aged 30–49 yr in Women's Lifestyle and Health Study** Exposed: 6801 Unexposed: 8013 Recruitment period: 1990–1991	0.7	0.4 to 1.4	Age, BMI, smoking, education, alcohol intake, physical activity, history of hypertension, history of diabetes, menopausal status	Norway, Sweden	Fair	1
Lidegaard, 2012[329]	**Women aged 15–49 yr in Denmark** Exposed: 4,651,766 person-years Unexposed: 9,336,662 person-years Recruitment period: 1995–2009	NR	NR	Age, education, year, risk factors	Denmark	Fair	3

Table 55. Study characteristics and association between OC use and myocardial infarction incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Pooled							
Sidney, 1998[336] Sidney, 1996[335]	**Women aged 15–44 yr in pooled data from Kaiser Permanente Medical Care Program and University of Washington** Cases: 166 MI, Kaiser Permanente members and 101 MI, University of Washington patients Controls: 479 no MI, Kaiser Permanente members and 512 no MI, community Recruitment period: 1991–1995	0.94	0.40 to 2.20	Age, race, BMI, smoking, education, menopause, whether treated for hypertension or diabetes	U.S.	Good	1

BMI = body mass index; CI = confidence interval; NA = not applicable; NR = not reported; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Meta-analysis code: 1 = Included in this meta-analysis of current versus noncurrent OC use; 2 = Excluded due to current versus noncurrent OR not reported; 3 = Adjusted relative risks as calculated from person-years of exposure cannot be converted to odds ratios.

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Current Versus Noncurrent OC Use

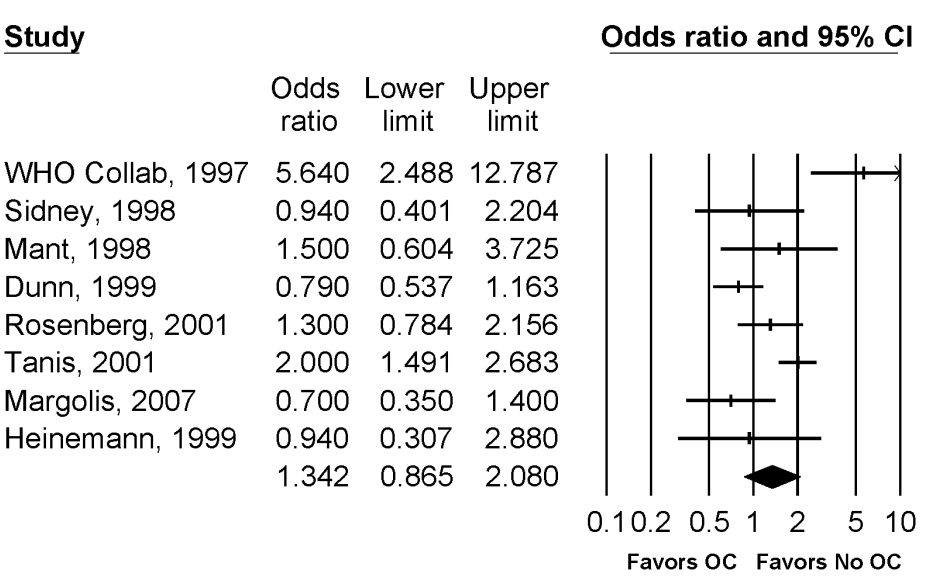
Eight studies[265,272,336,337,339-342] were included in this meta-analysis examining the effect of current versus noncurrent OC use on MI incidence. Of these, five were case-control studies representing 1772 cases and 7057 controls, two were cohort studies representing 310,626 person-years and 14,814 people, and one was a pooled analysis representing 267 cases and 991 controls.

The pooled analysis[336] was included in the meta-analysis rather than its individual case-control report.[335] The pooled analysis included previously unpublished data on 104 additional patients from a second site using identical methods and analysis as the case-control report, and therefore the pooled patient-level analysis provided the greatest evidence concerning current versus noncurrent OC use and myocardial infarction.

Five studies were rated good quality and three fair quality. Two studies[336,340] included patients from the United States; the remaining studies were either fully or partially based in Europe or the United Kingdom. Abstracted data not included in this meta-analysis are specified (with rationale) in Table 55. Reasons include not reporting a current versus noncurrent odds ratio and not providing data in a format that can be converted to an odds ratio.

Figure 38 shows the results of the meta-analysis. The odds ratio of MI among current versus noncurrent OC users was 1.34 (95% CI, 0.87 to 2.08) demonstrating a small increase in MI incidence among current OC users that did not reach statistical significance. There was significant heterogeneity, with a Q-value of 34.47 for 7 degrees of freedom, $p<0.001$. Most of the heterogeneity was from the WHO Collaborative study.[267,337] This study was unique in that it included participants from Africa, Asia, and Latin American in addition to Europe and the United Kingdom. No sensitivity analyses were performed because all included studies were fair or good quality, and only two studies[336,340] included participants from the United States.

Figure 38. Forest plot for current versus noncurrent OC use (myocardial infarction incidence)



CI = confidence interval; OC = oral contraceptive

Duration of OC Use

There were too few studies to perform a meta-analysis of the risk of MI by duration of current OC use. A large, fair-quality European cohort study[342] found no change in the relative risk of MI according to increasing duration of OC use for less than 5 years, 5 to 9 years, 10 to 14 years, or 15 years or more. In fair-quality cohort study from the United Kingdom,[265] ever users of OCs for up to 8 years had 1.9 times the risk of MI (95% CI, 1.0 to 3.5) compared with never users, while ever users for more than 8 years had no change in risk compared with never users (RR 1.0; CI, 0.6 to 1.8). However, in a later analysis of the same cohort,[165] there was no difference in ischemic heart disease mortality by the duration of ever use of OCs. This study is discussed in more detail in the section on OC use and MI mortality.

OC Formulation

Estrogen Dose

We investigated whether the dose of estrogen in OCs is related to risk of MI (high dose was ≥50 mcg of ethinyl estradiol and low dose was <50 mcg of ethinyl estradiol). One fair-quality cohort study[342] evaluated the risk of MI associated with low-dose versus high-dose estrogen and reported no difference in risk between these two groups (relative risks were not reported). A good-quality case-control study[267,337] evaluated the risk of MI associated with high-dose estrogen use in several European countries. They found a risk ratio of 7.69 (95% CI, 3.29 to 18.0) among users of high-dose estrogen OCs compared with nonusers and a risk ratio of 2.93 (CI, 1.23 to 6.97) for users of low-dose estrogen OCs. This study was unique in that it included populations from Africa, Asia, and Latin America.

Users of OCs containing no estrogen (i.e., progestin-only OCs) were found to have an odds ratio of 0.94 (95% CI, 0.31 to 2.91) for MI in one multinational case-control study.[272] In a second multinational case-control study,[267] progestin-only OC users were found to have an odds ratio of 0.98 (CI, 0.16 to 5.97).

Progestin Generation

Five case-control studies[261,270,338,340,341] were included in a meta-analysis examining the effect of current versus noncurrent OC use on MI incidence by progestin generation (Table 56). Three were rated good quality and two fair quality. Only one study[340] included patients from the United States. These five studies represented 1599 cases and 7276 controls. A good-quality, large cohort trial[329] reported adjusted relative risks of MI associated with progestin formulations across all four generations, but this study was not included in the meta-analysis because the relative risks could not be converted to odds ratios.

Table 56. Data for outcomes on progestin generation (myocardial infarction incidence)

Study[a]	Formulation[b] (Vs. Noncurrent OC Use)	OR	95% CI	Notes
First Generation				
Lidegaard, 1998[270]	First generation	4.8	2.1 to 11	
Dunn, 1999[338]	Noresthisterone	1.83	0.15 to 22.7	
Lewis, 1999[261]	First generation	4.66	1.52 to 14.33	
Tanis, 2001[341]	First generation	2.7	1.0 to 7.3	
Rosenberg, 2001[340]	Progestogen containing <50 mcg of norethindrone	2.5	1.1 to 5.5	Current vs. never use
Lidegaard, 2012[329]	Norethindrone/EE 50 mcg Norethindrone/EE 30-40 mcg Norethindrone (no estrogen)	2.74 2.28 0.81	1.51 to 4.97 1.34 to 3.87 0.42 to 1.56	Adjusted relative risk, based on person-years of exposure
Second Generation				
Lidegaard, 1998[270]	Second generation	1.8	0.8 to 4.3	
Dunn, 1999[338]	Levonorgestrel	0.93	0.45 to 1.95	
Lewis, 1999[261]	Second generation	2.99	1.51 to 5.91	
Tanis, 2001[341]	Second generation	2.5	1.5 to 4.1	
Rosenberg, 2001[340]	Progestogen containing <50 mcg levonorgestrel	1.6	0.5 to 5.2	Current vs. never use
Lidegaard, 2012[329]	Levonorgestrel/EE 50 mcg Levonorgestrel/EE 30-40 mcg Levonorgestrel (no estrogen)	4.31 2.02 0	3.09 to 6.00 1.63 to 2.50 0.00 to 35.01	Adjusted relative risk, based on person-years of exposure
Third Generation				
Lidegaard, 1998[270]	Third generation	1.1	0.5 to 2.5	
Dunn, 1999[338]	Third generation Desogestrel Gestodene	1.66 1.20 2.41	0.75 to 3.67 0.40 to 3.57 0.80 to 7.30	
Lewis, 1999[261]	Third generation	0.85	0.30 to 2.39	
Tanis, 2001[341]	Third generation	1.3	0.7 to 2.5	
Lidegaard, 2012[329]	Norgestimate/EE 30-40 mcg Desogestrel/EE 30-40 mcg Gestodene/EE 30-40 mcg Desogestrel/EE 20 mcg Gestodene/EE 20 mcg Desogestrel (no estrogen)	1.33 2.09 1.94 1.55 1.20 1.46	0.91 to 1.94 1.54 to 2.84 1.62 to 2.33 1.13 to 2.13 0.77 to 1.85 0.55 to 3.90	Adjusted relative risk, based on person-years of exposure
Fourth Generation				
Lidegaard, 2012[329]	Drospirenone/EE 30-40 mcg Cyproterone/EE 30-40 mcg Drospirenone/EE 20 mcg	1.65 1.47 0	1.03 to 2.63 0.83 to 2.61 0.00 to 12.99	Adjusted relative risk, based on person-years of exposure

CI = confidence interval; EE = ethinyl estradiol; OC = oral contraceptive; OR = odds ratio

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]First-generation progestins = norethindrone and ethynodiol diacetate; second-generation = levonorgestrel and norgestrel; third-generation = gestodene, desogestrel, and norgestimate; fourth-generation = drospirenone, dienogest, and cyproterone acetate.

Table 57 lists the results for the meta-analysis of MI odds by progestin generation. MI risk appears to be highest among first generation progestin users. The formal test for difference gives a chi-square value of 8.78 for 2 degrees of freedom, p=0.0125. There is no significant heterogeneity. The estimated value of σ is 0.0.

Table 57. OC progestin generation and myocardial infarction risk in current OC users compared with nonusers

Generation	Odds Ratio (95% Confidence Interval)
First	3.37 (2.04 to 5.54)
Second	1.79 (1.16 to 2.75)
Third	1.34 (0.91 to 1.98)

Most of the risk ratios reported by Lidegaard et al.[329] across all four generations of progestins seemed to show no increased risk of MI by progestin generation, pointing instead to a possible increased risk of MI with increasing estrogen dose.

Special Populations

Cardiovascular Risk Factors

Age, Diabetes, Hypertension, Dyslipidemia

There was insufficient information to perform a meta-analysis evaluating the risk of MI among users of OCs with cardiovascular risk factors, but several studies did provide information regarding this question. In a large, fair-quality European cohort study,[342] the risk ratio of MI was not elevated among former or current users of OCs, and there was no effect modification by age, hypertension, or diabetes status. The only group with a significant elevated risk of MI were women who had ever been advised by a physician to stop OCs (RR, 1.4; 95% CI, 1.0 to 2.1). A good-quality European case-control study[341] found an elevated risk of MI among ever users of OCs in all age categories. There was no reported statistical difference according to age. The risks of MI were highest among OC users who were smokers or who had hypertension, hypercholesterolemia, diabetes, or obesity. In some cases, the risks appeared to be multiplicative.

Smoking

In a fair-quality U.K. cohort,[265] the risk of MI was not elevated in OC users who were nonsmokers, OC nonusers who were smokers, or OC users who smoked less than 15 cigarettes per day. However, compared with never users, the risk of MI increased four-fold among smokers of 15 or more cigarettes per day whether they were former users (RR, 4.0; 95% CI, 1.3 to 16.2) or current users (RR, 4.9; CI, 1.2 to 23.6). A good-quality U.S. case-control study[340] had similar findings; the odds of MI associated with current OC use were not elevated in those who smoked 1 to 25 cigarettes a day. However, the odds were elevated for nonusers who smoked more than 25 cigarettes a day (OR 12; CI, 9 to 16) and significantly more elevated for current users of OCs who smoked more than 25 cigarettes a day (OR 32; CI, 12 to 81; p=0.05). A third fair-quality U.K. case-control study[339] found no interaction between smoking and use of OCs on the risk of MI; in this study, the definition of "nonusers" is not clear.

Blood-clotting Disorders

A good-quality European case-control study[341] evaluated the relationship between inherited clotting disorders and the risk of MI. With a reference group of nonusers with no Factor V Leiden or prothrombin G201210A mutation, the estimated odds ratios were 1.4 (95% CI, 0.7 to 2.7) for nonusers with a mutation; 2.1 (CI, 1.5 to 3.0) for OC users without a mutation; and 1.9 (CI, 0.6 to 5.5) for OC users with a mutation. These findings suggest that there is no interaction between Factor V Leiden or prothrombin G20210A carrier status and OC use upon the odds of MI.

OC Use and Myocardial Infarction Mortality

We identified three cohort studies[33,164-166,334] evaluating the risk of MI mortality in OC ever users versus never users that could be combined into a meta-analysis (Table 58). These studies represent 46,112 participants in one study and 3,091,673 person-years in the other two. Two of the studies were based in the United Kingdom and one in China. The U.K. studies recruited women in the 1960s and 1970s[33,165] and were fair quality. The study in China was poor quality.

A fourth study[343] reported on the relationship between OC use and MI mortality. We did not include this secondary analysis of a case-control study[338] conducted in the United Kingdom in the meta-analysis because the reference group and the definition of OC use differed from the other three studies. This poor-quality study compared 148 women who died within 28 days of an MI to 24 women who died more than 28 days after an MI plus 413 MI survivors. The authors reported adjusted ORs of 0.83 (95% CI, 0.25 to 2.81), 2.88 (CI, 1.22 to 6.77), and 0.89 (CI, 0.27 to 2.92) for third-generation OC use, second-generation OC use, and other OC use, respectively, compared with no OC use, with OC use in all cases being defined as OC use the 3 months prior to the MI.

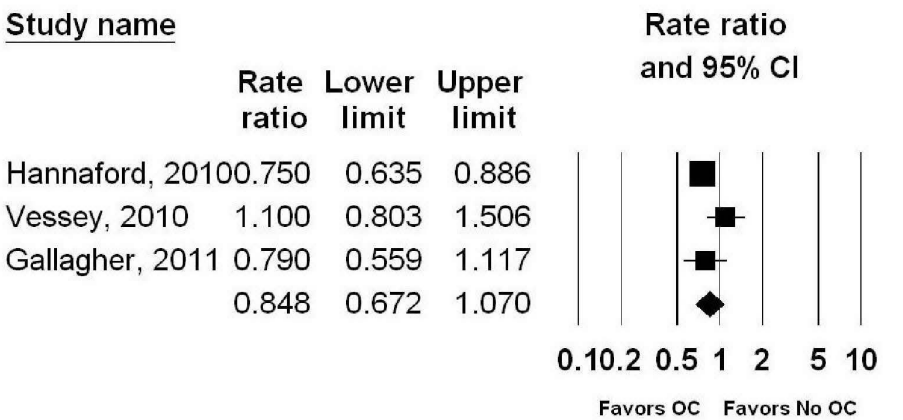
Table 58. Study characteristics and association between OC use and myocardial infarction mortality

Study	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[a]
Case-control (continued)							
Dunn, 2001 #1726[343]	**Women aged 16-44 from the Myocardial Infarction Causality study** Cases: 148 who died within 28 days of an MI Controls: 24 who died more than 28 days after an MI and 413 MI survivors Recruitment period: 1993—1995	NR	NR	NA	UK	Poor	2
Cohort							
Hannaford, 2010[33]	**Royal College of General Practitioner's Oral Contraception study** Exposed: 28,806 Unexposed: 17,306 Mean age at study entry: 29 (SD 6.6) Recruitment period: 1968–NR	NR	NR	NA	UK	Fair	1
Vessey, 2010[165]	**Women aged 25–39 yr in Oxford Family Planning Association Contraceptive Study** 602,700 person-years (total for exposed and unexposed) Recruitment period: 1968–1974	NR	NR	NA	UK	Fair	1
Gallagher, 2011[334]	**Female workers in 526 textile factories in Shanghai** Exposed: 366,890 person-years Unexposed: 2,122,083 person-years Recruitment period: 1989–1991	0.79	0.56 to 1.12	Age	China	Poor	1

CI = confidence interval; NA = not applicable; NR = not reported; OR = odds ratio; SD = standard deviation; UK = United Kingdom; yr = year/years
[a]Meta-analysis code: 1 = Included in meta-analysis; 2 = Excluded due to difference in reference group and definition of OC use.

The results of a meta-analysis of these three studies of MI mortality as a function of oral contraceptive use are shown in Figure 39 The random-effects estimated odds ratio is 0.85 (95% CI, 0.67 to 1.07). There was some evidence of heterogeneity, with a Q-value of 4.48 for 2 degrees of freedom, p=0.107. Of note, the risk of MI mortality trended higher among current users (as opposed to ever users) in the Chinese cohort (OR 2.38), but the finding was not statistically significant (CI, 0.58 to 9.76).

Figure 39. Effect of OC use on myocardial infarction mortality



CI = confidence interval; OC = oral contraceptive

Strength of Evidence for OC Use and Risk of Myocardial Infarction

Table 59 shows the strength of evidence for the effect of OC use on the risk of myocardial infarction.

Table 59. Strength of evidence domains for the effect of OC use on myocardial infarction

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Myocardial Infarction						
Current vs. noncurrent use/never	8 (24,901 plus 310,626 person-years)	Medium	Inconsistent	Direct	Imprecise	Low 1.34 (0.87 to 2.08)
Estrogen	2 (15,903)	Medium	Consistent	Direct	Imprecise	Insufficient NR
Progestin	5 (8875)	Medium	Consistent	Direct	Precise	High First generation: 3.37 (2.04 to 5.54) Second generation: 1.79 (1.16 to 2.75) Third generation: 1.34 (0.91 to 1.98)
Mortality From Myocardial Infarction						
Current vs. noncurrent use/never	3 (46,112 plus 3,091,673 person-years)	Medium	Inconsistent	Direct	Imprecise	Low 0.85 (0.67 to 1.07)

CI = confidence interval; SOE = strength of evidence

Discussion

We found strong evidence of a three-fold increased risk of VTE among current users of OCs and a two-fold increased risk of ischemic and undifferentiated stroke among current users of OCs. We found no conclusive evidence of an increased risk of MI or hemorrhagic stroke. The implications of OC use for each of these outcomes are discussed in detail below.

OC Use and Venous Thromboembolism

We found a three-fold increase in the odds of VTE diagnosis among current users of OCs (95% CI, 2.46 to 3.59). There was significant heterogeneity among the study characteristics and among the risk estimates noted by the Q scores. However, the finding was robust in our sensitivity analysis and was almost identical to the findings in a recent meta-analysis.[43] The odds ratio for VTE among current versus noncurrent OC users in that analysis was 3.41 (95% CI, 2.98 to 3.92). They analyzed 55 manuscripts, of which 32 were included in their meta-analysis of current versus noncurrent OC use and VTE risk. These manuscripts overlapped with 9 studies in our meta-analysis of 14 studies. The authors included all studies indexed in MEDLINE, Embase, and HealthSTAR regardless of date of publication. The odds of developing PE specifically appeared to be similar to that of developing VTE. The increased risk of DVT associated with OC use appears to be due to current use and not ever use. The only study to report a significantly increased risk among ever users also included current users in that group. The three studies that

separately analyzed former and current use of OCs found increased odds of VTE for current users but not for former users.

Duration and Formulation

There was some evidence that the risk of VTE among current users was higher in the first few years of use. Manzoli et al.[43] found a pooled odds ratio of 5.28 (95% CI, 4.27 to 6.55) for those who had used OCs for less than 1 year, and a pooled odds ratio of 3.52 (CI, 2.83 to 4.37) for those who had used OCs for more than 1 year. One potential explanation for this finding is that some women who develop VTE while on OCs may have an undiscovered predisposition to blood clots. Therefore, they develop VTE quickly after initiation of OC use, while women who are on OCs for years without forming a VTE presumably are less likely to have a predisposition to blood clotting. On the other hand, many factors that predispose women to blood clots will vary over time (e.g., trauma, sedentary lifestyle, and antiphosopholipid antibodies) and these risk factors have not been studied in a longitudinal fashion.

We found inconclusive evidence that estrogen dose or progestin generation was associated with VTE risk among current users of OCs. However, Manzoli et al.[43] found a mildly increased risk of VTE among current users of high-dose versus low-dose estrogen (OR 1.42; 95% CI, 1.15 to 1.76). They also found an increased risk for third-generation versus second-generation progestin users (OR 1.57; CI, 1.24 to 1.98). However, as was similar with our findings, they did not find an increased risk of VTE among drospirenone users compared with other OC users. This question has generated recent media attention since several studies indicated an increased risk of DVT among users of OCs containing fourth-generation progesterones.

Special Populations

There may be a multiplicative relationship in the risk of VTE among users of OCs who had concomitant Factor V Leiden, sickle cell trait, or elevated homocysteine levels; however ,these findings would need to be confirmed in additional studies.

Clinical Application

The three-fold increased odds of VTE among current users of OCs is important given the life-threatening nature of VTE. The mortality rate of DVT in the general population is 5 percent within the first month after diagnosis; for PE, it is 12 percent within the first month after diagnosis.[344] However, these estimates come from cohorts that include males, older individuals, and patients with cancers or heart disease. Young, healthy women who take OCs likely have lower mortality rates, but there is a paucity of data addressing this question. In one cohort of patients from the United States with DVT or PE, the univariate hazard ratio of death within the first week after VTE diagnosis among OC users was 0.08 (95% CI, 0.03 to 0.26) compared with other patients with VTE.[345] The clinical significance of the increased incidence of VTE among OC users must also be understood in the context of the low prevalence of VTE in this population. The annual incidence of VTE among childbearing-age women is 2 to 3 per 10,000 people.[346] Therefore, a three-fold increased risk translates to a still low absolute risk of fewer than 10 per 10,000 people per year. Perhaps most importantly, the incidence of VTE is four times higher among pregnant or postpartum women than among nonpregnant women. Therefore, the VTE risks associated with using OCs to prevent pregnancy are thought to be outweighed by the benefits of preventing pregnancy. Our findings will be used in a Markov model that estimates the overall risks and benefits of OC use for the prevention of ovarian cancer.

OC Use and Stroke

We found a two-fold risk of both undifferentiated and ischemic stroke among current OC users, but no increased risk of hemorrhagic stroke. As with VTE, this risk seemed to be due to current and not ever use. Many of the studies that evaluated the relationship between OC use and stroke did not differentiate between hemorrhagic and ischemic stroke. Since most cerebral vascular accidents have an ischemic etiology, we combined studies of patients with known ischemic stroke and studies of undifferentiated stroke. To the extent that studies of undifferentiated stroke included hemorrhagic patients, this approach would be expected to underestimate the true association between OC use and ischemic stroke.

Duration and Formulation

We found inconclusive evidence that the risk of stroke changed with duration of OC use or progestin generation. There was, however, evidence that the risk of stroke increased with increasing estrogen dose (from 1.7 to 4.1). This evidence was confirmed by trials of progestin-only OCs that showed no elevated ischemic stroke risk.

Special Populations

Women with migraines, Factor V Leiden, and elevated homocysteine levels who use OCs may have a multiplicative increase in the risk of stroke. However, these findings need to be confirmed in larger studies. Increasing age of OC users may be associated with increasing risk of ischemic stroke. However, these data also need to be confirmed in larger studies.

Clinical Implications

As with VTE, the two-fold risk of ischemic stroke is important because stroke is both life-threatening and morbid.[347] Between 8 to 12 percent of ischemic stroke victims die within one month of the diagnosis—and the vast majority have major neurologic deficits. Stroke is the leading cause of long-term disability in the United States. However, ischemic stroke incidence among women aged 15 to 44 is only 10.7 per 100,000 women-years[348] and, similarly to VTE, pregnant and postpartum women have a three- to eight-fold increased risk of ischemic stroke.[347] Therefore, the stroke risks associated with OC use are likely balanced by the benefits of preventing pregnancy. This may not be the case for women who are using OCs for ovarian cancer prevention and are not planning pregnancy.

OC Use and Myocardial Infarction

We found a small increased risk of MI among current OC users (1.2), but the confidence intervals were not significant. There was also inconclusive evidence that duration of OC use or estrogen dose increased the risk. However, we did note a significant increased risk for first-generation progesterone users compared with second-and third-generation users. There may be a small increased risk of MI among current OC users that our meta-analysis is underpowered to find. This risk may be greater among specific groups, such as users of first-generation progestins, heavy smokers (15 cigarettes or more daily), or women with cardiovascular disease risk factors.

Notably, one study found a decreased mortality from MI among ever users of OCs. Reasons for this could be decreases in competing risks associated with pregnancy, bias of ascertainment in women who were known OC users, or decreased prescribing of OCs to women with

cardiovascular disease risk factors. These issues may not have been fully adjusted for in the analysis.

Clinical Implications

For now, there is inconclusive evidence about increased MI risk associated with current OC use. Like VTE, MI is rare in women of reproductive age. In the United States, the annual incidence of MI is 0.3 to 0.7 percent among women; however, it is the sixth leading cause of death. Additional evidence is needed to effectively counsel patients about the risk of MI associated with OC use.

Limitations

The major limitation to our findings is the lack of randomized trials available to determine if OCs cause increased risk of VTE, stroke, or MI. Of the studies included, the majority were case-control studies, likely due to the relative rarity of the outcomes in young women. Observational data are limited by unmeasurable confounding and inability to establish causation.

A second limitation of these data is the high degree of heterogeneity among the studies. There were many differences across studies in the covariates used in the analyses to adjust for potential confounding. For example, few studies of stroke incidence adequately controlled for well-established stroke risk factors such as hypertension, diabetes, and hyperlipidemia. The outcome definitions were also heterogeneous between studies. In the case of VTE, several studies included central venous thrombosis and superficial venous thromboembolism despite the fact that VTE is traditionally defined as DVT and/or PE. Further, some investigators excluded "nonidiopathic" or unexplained DVT from the analysis, but the majority did not. In the case of stroke, some investigators included central venous thrombosis, and transient ischemic attacks in the definition of stroke. Others did not differentiate between ischemic and hemorrhagic stroke.

Finally, the definition of the exposure varied by studies. A minority of studies compared ever OC users with never users. The majority of studies used current OC use as the exposure; however, many different definitions of current use existed (e.g., recently filled prescriptions, reported use in the last 3 months, or reported use in the last month). We included all studies that defined current use as sometime within the year prior to outcome assessment. The referent group also varied. In some cases, this was never users and in others this was noncurrent users, which included past and never users.

A limitation for all our formulation analyses is the large number of OC formulations that have been available during the course of these studies. Not only is it difficult to correctly identify a formulation used, but it is also impossible to know if that formulation was the one most proximal to an outcome of interest. Women taking OCs frequently change formulations due to cost or side effects, and so the formulation identified may not have been the one that should have been associated with the event. In addition, estrogen dose is not independent of progestin generation. Most higher dose estrogens are only found in combination with earlier generation progestins. We were unable to control for this in the analysis. Even if there were enough data to compare risks across formulations, the sheer volume of formulation combinations would cause a problem with multiple testing. Finally, current OC prescribing patterns in the United States involve mostly "very low dose" estrogen (e.g., 20 mcg or less); this dose of estrogen was infrequently reported in the included studies, and the risk associated could not be analyzed separately.

For each of the outcomes of interest, increasing age is associated with increased risk in the general population. Although every study corrected for age of the participant in the analysis, there were few studies that assessed the risk of each outcome in current OC users stratified by age. This information would be clinically meaningful when counseling patients. The age of participants is very integral to the risk–benefit calculation of using OCs to prevent ovarian cancer. For example, very few women over age 35 use OCs for contraception; therefore, this age group is probably underrepresented in the current data. However, this is the very age group that may be interested in using OCs for prevention of ovarian cancer.

Future Research

Given the increased risk of VTE and stroke among OC users, future randomized controlled trials (RCTs) are unlikely. However, it would be useful if women who participated in RCTs of OC use investigating other outcomes could be followed to determine long-term risk of VTE, stroke, and MI. Future observational research into the risk of acute vascular complications associated with OC use should (1) clearly define the outcome of interest (e.g., ischemic vs. hemorrhagic stroke, not including transient ischemic attacks), (2) define the exposure as current versus never use and former versus never use and clearly define "current use," (3) adjust for all known risk factors of the outcome (e.g., hypertension), (4) collect duration data according to years of use instead of categories so that more detailed analysis could be undertaken, (5) collect data on contemporary OCs such as very low dose estrogen pills, and (6) prioritize longitudinal cohort data. Studies addressing the risk of MI among current users of OCs are needed most.

Applicability

The most important applicability issues are the time period of study for some of the large studies (going all the way back to the 1960s, with subsequent problems around dissimilar OCs used then vs. used now) and that very few of the included studies were conducted in the United States. Inadequate or incomplete reporting of age-related variables (e.g., age at first use of OCs, age at time of outcome event, and age at time of study participation) also contribute to the difficulty in applying these findings to specific age-groups of women in the United States.

Section 5. Overall Benefits and Harms of Oral Contraceptives for Prevention of Ovarian Cancer

Background

Our systematic review and evidence synthesis found significant protective effects of oral contraceptives (OCs) against ovarian cancer, in both the general population and in high-risk groups such as BRCA1 and BRCA2 carriers, with risk decreasing as the duration of use increases. We also found significant decreases in the risk of colorectal and endometrial cancers. Increased risks were significant for breast cancer (with risk declining with time since last use), deep venous thrombosis (DVT), pulmonary embolism (PE), and ischemic stroke. The incidences of myocardial infarction (MI) and cervical cancer were also increased, although the confidence interval for these two associations included 1.0.

There has long been recognition that OC use has important noncontraceptive implications for health.[349] Previous studies using formal methods to synthesize the available data in order to estimate net effects have generally shown either no overall effect, or a small positive effect, particularly for younger women.[66,350,351]

Relevant Key Questions

The seven KQs developed for the entire systematic review are listed in Section 1 (refer to Figure 7 for a roadmap of this report). For Section 5, we have developed a new simulation model to generate estimates of the net harms and benefits of OC use in order to examine the following KQs:

KQ 4: Aside from pregnancy prevention, are there other benefits of OC use in reducing the risks of endometrial cancer or colorectal cancer?

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

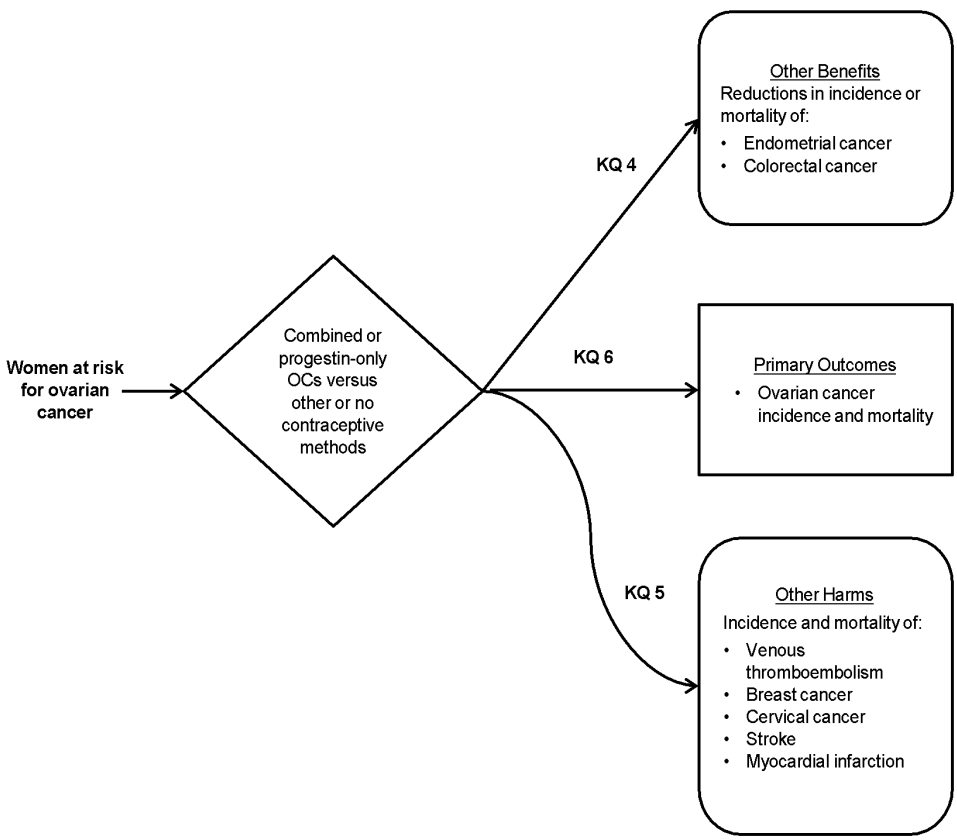
KQ 6: Based on the comprehensive literature review, what are the benefits and harms from the use of OCs to reduce the incidence of ovarian cancer for specific populations? Based on the decision model, what is the estimated effect of these benefits and harms on life expectancy and quality-adjusted life expectancy?

KQ 7: Based on the systematic review and decision model, what research gaps need to be filled to better understand whether OCs are effective for the primary prevention of ovarian cancer?

Analytic Framework

Figure 40 shows the analytic framework that guided this section of the review.

Figure 40. Analytic framework for overall benefits and harms of OCs



KQ = Key Question; OC = oral contraceptive
Note: KQ 7 is not shown in the analytic framework.

Methods

A detailed description of the simulation model structure, data sources, and parameters is provided in Appendix F. Section 5 summarizes those aspects most relevant to the presented results. Unless otherwise noted, we used national estimates from 2007—the most recently available at the start of the model-construction process.

Age-Specific Incidence of Relevant Outcomes With and Without OC Use

We obtained estimates of the age-specific (in 5-year age groups) incidence of ovarian, breast, cervical, colorectal, and endometrial cancers from two sources: (1) the Surveillance, Epidemiology, and End Results (SEER) database maintained by the National Cancer Institute (http://seer.cancer.gov/canques/index.html) and (2) the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries (http://wonder.cdc.gov/wonder/help/cancernpcr-v2009.html). Estimates were derived for all women as well as for four mutually exclusive race/ethnicity classifications: non-Hispanic white, non-Hispanic black, non-Hispanic other, and Hispanic. For the simulation model, we used age-specific and race/ethnicity-specific estimates of the number of cases and the total number of women in each strata from U.S. Census estimates (www.census.gov/popest/data/intercensal/national/nat2010.html) to generate beta distributions for incidence.

Estimates for the age-specific and race/ethnicity-specific incidence of DVT, PE, stroke, and acute MI were derived from the 2007 Nationwide Inpatient Sample (NIS), using specific International Classification of Disease-9 (ICD-9) codes as detailed in Appendix F. Again, distributions for stochastic modeling were derived by generating gamma distributions based on point estimates and standard errors and dividing by the estimated number of females in each strata based on Census estimates.

Estimates for the usage history of OCs were obtained from the National Survey of Family Growth (NSFG) data for 2002[352] and 2006 (www.cdc.gov/nchs/nsfg/nsfg_2006_2010_puf.htm).

For current exposure to OCs, we estimated age-specific and race/ethnicity-specific prevalence of current use of OCs as reported by survey respondents; for ever OC use, we used the cumulative estimate of race/ethnicity-specific self-reported ever use by age 44 in the 2006 NSFG. We derived estimates of the age-specific probability of beginning OC use for the first time from the age-specific prevalence of ever use within each racial/ethnic group.

We then estimated the impact of current OC use and ever OC use on the five cancers and four vascular events from the age-specific incidence estimates, the age-specific exposure estimates for OCs, and the derived odds ratios from the meta-analyses reported earlier. For any outcome,

Overall Incidence = (Incidence in OC users) * (Prevalence OC use) + (Incidence in nonusers) * (Prevalence nonuse).

since

Incidence in OC users = (Incidence in nonusers) * (Relative risk in OC users),

and

Prevalence nonuse = 1 – (Prevalence OC use),

separate estimates for age-specific incidence in users and nonusers can be derived from the overall incidence (converted to probabilities as described in Appendix F), the prevalence of OC use, and the relative risks (estimated here from the odds ratios from the respective meta-analyses).

Table 60 shows the relative risk estimates for the association between OC use and incidence of outcomes of interest (relative risks estimated based on odds ratios). All estimates except for the joint effect of duration of OC use and time since last use are derived from the meta-analyses

described in Sections 2–4 of this report. These estimates reflect the results of our initial analyses completed for the initial version of the report; as described in the methods, these analyses were updated during peer review. Because the estimates and confidence intervals are essentially unchanged, we present the results of the more extensive analyses completed with the original estimates. The one substantive change was that time since last use was found to have a significant effect on the protective association between OC use and ovarian cancer risk, with protection decreasing with increasing time since last use. Because the study-level meta-analyses did not allow for estimating the distribution of duration of OC use and time since last use, we used stratified data from a single published pooled analysis.[21] Because the pooled analysis had insufficient observations to generate estimates for risks for durations of use greater than 5 years with last use 30 or more years previously, we used the estimates for 20 to 29 years. We assumed that OC use had no effect on survival after diagnosis of cancer or a vascular event since the literature review did not identify a significant effect of OCs on postdiagnosis survival. Therefore, any effects of OC use on cancer-specific or vascular event-specific mortality generated by the model are due only to effects on incidence.

Table 60. Relative risk estimates for association between OC use and incidence of outcomes of interest

Parameter	Base Case Estimate	Range (95% CI Unless Otherwise Specified)	Distribution Type
Cancers (Ever vs. Never OC Use)			
Ovarian			
General population	0.71	0.64 to 0.79	Lognormal
BRCA1 carrier	0.54	0.45 to 0.65	Lognormal
BRCA2 carrier	0.60	0.29 to 1.54	Lognormal
Breast			
General population	1.08	1.01 to 1.15	Lognormal
BRCA1 carrier	1.18	0.92 to 1.50	Lognormal
BRCA2 carrier	1.18	0.92 to 1.50	Lognormal
Cervical	1.28	0.89 to 1.86	Lognormal
Colorectal	0.86	0.79 to 0.95	Lognormal
Endometrial	0.55	0.42 to 0.70	Lognormal
Cancers (Other Exposure Types)			
Duration of OC use and ovarian cancer risk	1 - 1 / (1 + 7.43 / duration (years))**1.239		Function
Time since last OC use and breast cancer risk	1 + (0.2711 * EXP(-0.06551 * years)		Function

Table 60. Relative risk estimates for association between OC use and incidence of outcomes of interest (continued)

Parameter	Base Case Estimate	Range (95% CI Unless Otherwise Specified)	Distribution Type
Joint Effect of Duration of OC Use and Time Since Last Use and Ovarian Cancer Risk			
Current or <10 Years Since Last Use			
Duration of use <5 years	0.88	0.75 to 1.04*	Lognormal
Duration of use 5–9 years	0.52	0.43 to 0.64*	Lognormal
Duration of use ≥10 years	0.39	0.33 to 0.47*	Lognormal
Last use 10–19 Years Previously			
Duration of use <5 years	0.85	0.62 to 0.73*	Lognormal
Duration of use 5–9 years	0.62	0.53 to 0.73*	Lognormal
Duration of use ≥10 years	0.51	0.44 to 0.59*	Lognormal
Last Use 20–29 Years Previously			
Duration of use <5 years	0.81	0.74 to 0.89*	Lognormal
Duration of use 5–9 years	0.69	0.60 to 0.78*	Lognormal
Duration of use ≥10 years	0.60	0.51 to 0.72*	Lognormal
Last Use ≥30 Years Previously			
Duration of use <5 years	0.83	0.73 to 0.95*	Lognormal
Duration of use 5–9 years	0.69	0.60 to 0.78*	Lognormal
Duration of use ≥10 years	0.60	0.51 to 0.72*	Lognormal
Vascular Events (Noncurrent vs. Current OC Use)			
Deep vein thrombosis	3.01	2.47 to 3.68	Lognormal
Pulmonary embolism	1.61	1.26 to 2.05	Lognormal
Stroke	2.02	1.11 to 3.65	Lognormal
Myocardial infarction	1.24	0.75 to 2.04	Lognormal

BRCA = breast cancer genetic mutation; CI = confidence interval; OC = oral contraceptive
*99% confidence interval.

Impact of Current Use Patterns of OCs on Overall Life Expectancy and Disease-Specific Incidence and Mortality

We developed a semi-Markov state-transition model using TreeAge Pro (Williamstown, MA: TreeAge, Inc.) to simulate the effects of use and nonuse of OCs on incidence and mortality from ovarian cancer and the other outcomes of interest (Appendix F). The model is run as a microsimulation, starting at age 10. During each iteration of the simulation, individual "subject" characteristics, including race/ethnicity and BRCA status are drawn from distributions (second-order Monte Carlo simulation). Depending on the simulation, the values of other parameters are either the base case estimate or a value drawn from the appropriate distributions described in Tables 60 and 61 (first-order Monte Carlo simulation). Cycle lengths are 1 month.

Table 61. Key parameter values, ranges, and distributions

Parameter	Base Case Estimate	Range (95% CI Unless Otherwise Indicated)	Distribution Type	Reference
Demographics/Natural History				
Race/ethnicity at age 10	Non-Hispanic: White: 56.9% Black: 14.9% Other: 7.9% Hispanic: 20.3%	Census data—assumed to have negligible uncertainty	Fixed	Census
BRCA1				
Prevalence	0.22%	0.15-0.33%	Beta	John, 2007[353] Anonymous 2000[354]
RR Ovarian cancer	41.7	30.1-53.3	Lognormal	Anonymous 2000[354]
RR Breast cancer	Age-dependent 20–39: 58.6 40–49: 14.4 50–99: 1.0	Age-dependent 20–39: 49.9-67.2 40–49: 0.9-28.0) 50–99: 1.0	Lognormal	Anonymous 2000[354]
BRCA2				
Prevalence	0.15%	0.08-0.23%	Beta	John, 2007[353] Anonymous 2000[354]
RR Ovarian cancer	9.9	2.3-17.4	Lognormal	Anonymous 2000[354]
RR Breast cancer	Age-dependent 20–39: 17.1 40–49: 11.2 50–99: 22.4	Age-dependent 20–39: 17.1 (9.7-24.5) 40–49: 7.5-15.0 50–99: 18.1-26.8	Lognormal	Anonymous 2000[354]
Age-Specific Incidence				
Hysterectomy	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NIS
Oophorectomy	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NIS
Bilateral tubal ligation	Age- and race/ethnicity-dependent	See Appendix F	Beta	Chan, 2010[355] Whiteman, 2012[356]
Cancers	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NIS
Vascular events	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NIS
Mortality				
All-cause mortality	Age- and race/ethnicity-dependent	See Appendix F	Gamma (numerator)	NCHS[a]
Cancers	Age- and race-dependent (white/black only)	See Appendix F	Beta	SEER
Vascular events	Age- and race/ethnicity-dependent	See Appendix F	Beta	NIS

Table 61. Key parameter values, ranges, and distributions (continued)

Parameter	Base Case Estimate	Range (95% CI Unless Otherwise Indicated)	Distribution Type	Reference
Oral Contraceptive Use				
Age At First Use				
Natural history	Age- and race/ethnicity-dependent	See Appendix F	Dirichlet	NSFG
Prescription	Randomly assigned	15–45	Uniform	
Duration of Use				
Natural history	Mean 54.8 months	Standard deviation 41 months, range 1–240	Gamma	Chasan-Taber, 1996[357]
Prescription	Randomly assigned	1–240 months, partly dependent on age of starting (not continued past age 45)	Uniform	
Reduction in ovarian cancer incidence after tubal ligation	0.69 for 15 years, then 1.0	0.64 to 0.75	Lognormal	Cibula, 2011[17]

NCHS = National Center for Health Statistics; NIS = Nationwide Inpatient Sample; NSFG = National Survey of Family Growth; RR = risk ratio; SEER = Surveillance, Epidemiology, and End Results

[a]http://wonder.cdc.gov/wonder/help/cmf.html#Compressed%20Mortality%20File:%20ICD%20Revision

The use of probabilistic analysis and microsimulation offer two main advantages over a deterministic approach. First, probabilistic analysis allows the model to incorporate both the range of uncertainty in parameter estimates (e.g., the width of a 95% confidence interval) as well as the distribution of that uncertainty. For example, for a given mean parameter value with a normal distribution around that mean, the model can be run multiple times, drawing from the distribution with most of the values lying close to the mean value, but 2.5 percent would be drawn from below the lower 95-percent confidence bound and 2.5 percent from above the upper 95-percent confidence bound). Using distributions can be particularly helpful for parameters that are not "statistically significant" using conventional criteria, but where the weight of the existing evidence suggests a trend. For example, if a point estimate for a relative risk is 1.6 with a 95-percent confidence interval of 0.99 to 2.3, the traditional interpretation is that the observed increased risk is not statistically significant. However, because it is only the lower tail of the distribution that is below 1.0, the probability that the risk is greater than 1.0 is more than 95 percent. From a decisionmaking perspective, quantifying these effects can be quite helpful—in some situations, a patient, clinician, or policymaker might want to consider the potential effects of an increased risk of harm if the probability of the harm truly being increased was more than 80 or 90 percent (depending on the absolute risk of harm and the consequences of that harm), even though a threshold based on "not statistically significant" would preclude consideration of that harm.

The main advantage of microsimulation for this specific application is that it allows the model to have "memory" so that the probability of the outcomes of interests can be conditioned not only on the current state but also on past events, such as past use of OCs or duration of OCs.

OC Use Scenarios

We modeled OC use under five scenarios; all scenarios began at age 10 and continued until death or age 100. Table 62 illustrates the main differences in the four OC-use scenarios. The

initial scenario included the full range of available contraceptive options as well as varying contraceptive effectiveness, pregnancy outcomes (including duration of pregnancy), and lactation. However, because of the paucity of data on the dynamics of contraceptive choice over a woman's lifetime, particularly in the United States, and because pregnancy is a potential competing risk for some outcomes, we elected to model "No OC use" by fixing the risk of the outcomes of interest to that of nonusers, based on the equations above. This allowed us to focus only on the potential tradeoffs between harms and benefits of OC use as a potential preventive agent.

Table 62. Five OC use scenarios used in model

Parameter/ Assumption	OC Use Scenario				
	Ever/Never	**Duration**	**No OC**	**Prescribed Duration and Age at First Use and Duration**	**Joint Effects of Duration and Time Since Last Use**
Age at first use	Age- and race-specific probability	Age- and race-specific probability	Age- and race-specific probability	Uniform distribution, assigned in sensitivity analysis	Age- and race-specific probability
Duration of OC use	Population distribution, constrained to stop by age 50	Population distribution, constrained to stop by age 50	Population distribution, constrained to stop by age 50	Uniform distribution, assigned in sensitivity analysis, constrained to stop by age 50	Population distribution, constrained to stop by age 50
Association between OC use and cancers	Relative risk based on ever vs. never use for all	Relative risk based on duration of use for ovarian cancer, time since last use for breast cancer, ever vs. never for others	No reduction or increase in risk associated with OCs; incidence assumed to be that of nonusers in general population	Relative risk based on duration of use for ovarian cancer, time since last use for breast cancer, ever vs. never for others	Relative risk based on duration of use and time since last use for ovarian cancer, time since last use for breast cancer, ever vs. never for others
Association between OC use and vascular events	Relative risk based on current vs. noncurrent use for all	Relative risk based on current vs. noncurrent use for all	No reduction or increase in risk associated with OCs; incidence assumed to be that of noncurrent users in general population	Relative risk based on current vs. noncurrent use for all	Relative risk based on current vs. noncurrent use for all

OC = oral contraceptive

Model Assumptions

We made a number of simplifying assumptions as described below. If an assumption could possibly bias the analysis for or against the potential benefits of OC use, we chose the more conservative assumptions that biased against potential benefits of OC use whenever feasible.

Excluded Other Potential Benefits and Harms

We did not include other potential benefits (e.g., prevention of pregnancy, effects on menstrual flow and discomfort, effects on other reproductive outcomes such as endometriosis or benign ovarian cysts, effects on acne or premenstrual syndrome) or harms (e.g., neoplasms of the liver, gallbladder disease). Although including the full range of potential benefits and harms is ultimately of great interest, the scope of this analysis was specifically restricted to the potential noncontraceptive preventive benefits of OCs. Therefore, we restricted our analysis to relatively common, potentially fatal cancers or vascular events for which a preliminary literature review suggested consistent evidence of an association with OC use.

Excluded Quality-of-Life Measures

We did not include quality-of-life measures. Although we originally intended to include quality-adjusted life expectancy, expressed as quality-adjusted life years (QALYs) as one of the outcomes, we were limited by a lack of available data on preferences for OC use. Although we identified several economic analyses of OC use for contraception—some of which included other outcomes,[350,358,359] or prophylaxis against ovarian cancer in BRCA1 and BRCA2 mutation carriers[360,361] which included utility values for outcomes relevant to our analysis—none included any values for OC use itself. There is a relatively high discontinuation rate of OC use within the first 12 months after starting, some of which is attributable to side effects.[362-366] Conversely, there are other potentially positive effects on quality-of-life, including effects on menstruation, reassurance against unwanted pregnancy, or reduced acne. Including only the effect of cancers and vascular events on QALYs could substantially bias overall estimates of the impact of OCs on quality-adjusted life expectancy. Therefore, we focused primarily on the specific balance between benefits (in terms of reduced cancers) and harms (in terms of increased cancers or acute vascular events); further work to integrate the effect of OCs, either as contraceptives or as prevention against other diseases, is a major research need.

Continuous OC Use for Duration

We assumed that, once "assigned" an age at first use and duration of use by the model, OC use would be continuous for that duration, then stopped. This is clearly not the case for most women, but because the available literature on duration of use does not distinguish between continuous and intermittent use, and data to inform patterns of use were not available, we used this simplifying assumption.

This assumption creates the potential for bias in both directions. In the case of breast cancer and vascular events, where incidence increases with age, an assumption of continuous use may underestimate the upper tail of the age distribution of current OC users, and therefore underestimate the potential increased risk associated with OC use. On the other hand, to the extent that time since last use potentially decreases protection for ovarian, colorectal, and endometrial cancers, underestimating the upper tail may lead to underestimating the protective effect, since the continuous use assumption results in longer average duration between last use and the time of highest cancer risk.

Point Estimates in Base-Case Analysis

For the purposes of the base-case analysis, we used the point estimates from the meta-analyses; since two of these (MI and cervical cancer) were not statistically significant using conventional criteria, this is a potential bias against OC use.

Analysis of Temporal Relationships

We included an analysis of temporal relationships such as age at first or last use, duration of use, or time since last use only for those found to be significant in the meta-analyses (duration of use and time since last use for ovarian cancer, and time since last use for breast cancer). Because the data available for meta-analysis did not allow for estimation of the joint effect of duration of use and time since last use, we used estimates for ovarian cancer risk stratified by both duration and time since last use from the pooled analysis of the Collaborative Group on Epidemiological Studies of Ovarian Cancer.[21] As discussed in Section 2, these estimates are quite similar to the results of the study-level meta-analyses. This was done primarily for tractability of modeling, and because estimates of relative risk were most commonly reported as ever vs never use. This assumption of lifetime effects for any duration exposure could result in overestimation of both benefits and harms.

Constant Risk of Vascular Events

We assumed that the risk of vascular events among current users was constant across time; i.e., that the degree of risk associated with OCs was the same during a woman's first and last month of use no matter how long. As discussed in Section 4, there is some evidence that the risk is highest early during use for some outcomes, particularly DVT,[281] presumably because women with an increased underlying risk such as inherited thrombophilias develop the outcome quickly. If this is the case, the assumption of constant risk may overestimate the likelihood of these events among all OC users.

We also assumed that there was no increased risk in vascular events after discontinuation of OCs. This was consistent with the findings for venous thromboembolism and stroke discussed in Section 4. Although we did not explicitly consider ever vs never use for myocardial infarction, another meta-analysis found no difference in risk between past users and never users.[47]

Survival After Cancer Diagnosis

We modeled survival after diagnosis for each cancer up to 5 years; after 5 years, we assumed cure (women with breast cancer were at risk for a second primary, although this was not conditioned on previous history). We limited followup for five years primarily because there is variability in reported length of followup between the different cancers. Particularly for breast cancer, where late recurrences are not uncommon, this may result in an underestimate of cause-specific mortality.

As described in Appendix F, survival after diagnosis was conditional on age at diagnosis and race (black vs. white only, with the assumption that survival for Hispanic and other-race women was identical to white women). Also as described in Appendix F, the model predictions for overall lifetime incidence when incorporating patterns of OC use and the derived estimates for the association between OC use and cancers showed good agreement with estimates of lifetime incidence derived from the SEER DevCan software. (http://surveillance.cancer.gov/devcan/).

Patterns of OC Use Over Lifetime

We found surprisingly few data on patterns of use of OCs over a woman's lifetime. Although we were able to generate an estimate of the distribution based on one study that reported a mean and standard deviation for duration,[357] the available literature does not provide any data to correlate duration of use with age of starting, and so we modeled these as independent

probabilities for those analyses where the values for these parameters were drawn from distributions.

We assumed no one would start OCs after age 45, (i.e., age at first use ranged from 12 to 44) age of first use to 44, based on data from the NSFG that showed almost no increase in the proportion of "ever users" after age 35, and the lack of available data for women over age 45 (since the NSFG only includes women aged 15 to 44 years). We also constrained duration of use so that all women stopped OC use at age 50, regardless of assigned age at first use and duration. Assuming that there is, in fact, a correlation between age at first use and duration of use, this assumption of independence may underestimate duration of use in younger women and overestimate it in older women. Particularly for vascular events, where overall risk increases with age and there is an assumption of constant risk with time among current users, this may result in an overestimate of the number of events in OC users.

Tubal Ligation

Because there is a consistent association between tubal ligation and reduced ovarian cancer risk, even after controlling for contraceptive use,[17,19,123,367] we included tubal ligation (based on age-specific and race/ethnicity-specific incidence and prevalence) in the model, and used the estimate for reduction in risk from a recent meta-analysis.[17] Because most studies of the association between ovarian cancer and OCs controlled for tubal ligation (and vice versa), we assumed that the risks were independent such that the risk of ovarian cancer in a woman with a history of OC use was further reduced if she subsequently underwent tubal ligation. We also assumed that the probability of tubal ligation was not conditioned on prior OC use.

Effect of Other Contraceptive Methods

Because the overwhelming majority of the literature classified OC use as some variant of ever versus never, we assumed that contraceptive methods other than tubal ligation that were used whenever OCs were not being used did not affect ovarian cancer risk, although one recent study suggests this may not be the case.[123]

Effect of Hysterectomy or Oophorectomy

Because removal of the potentially cancerous organ obviously affects the likelihood of developing cancer, we included age-specific and race/ethnicity-specific probabilities of hysterectomy and oophorectomy (in various combinations) in the model. We assumed that the risk of cervical and endometrial cancer was zero after hysterectomy and that the risk of ovarian cancer was zero after bilateral oophorectomy. Although there are fairly consistent data showing that women who undergo hysterectomy alone, without removal of the ovaries, have a reduced risk for ovarian cancer,[19,368] we assumed hysterectomy alone did not affect ovarian cancer risk, primarily because of uncertainty about potential interactions with OC use. Because OCs may reduce the incidence of both benign and malignant indications for hysterectomy, they could potentially decrease hysterectomy rates.

Conversely, because OCs may be prescribed for many conditions that can lead to hysterectomy, use of OCs may be associated with increased hysterectomy rates. This is consistent with data from two observational studies; in Denmark, a country with high overall use of OCs, long-term OC use was associated with decreased hysterectomy rates, while short-term use was associated with increased rates,[369] and in Ireland, where OC use for contraception was historically quite low, a history of OC use was associated with an increased hysterectomy rate.[370]

Three Types of Simulations

With the above assumptions and base-case estimates, we ran three types of simulations:

1. *Simple simulations,* where the mean value of the relative risks associated with OC use was used for all iterations. These included:
    a. A series of 60,000 simulations for the general population (all women including BRCA1 and BRCA 2 carriers) and 20,000 each for BRCA1 and BRCA2 carriers where the effect of OC use based on current use patterns was compared with no use.
    b. A series of 50,000 simulations for the general population and 20,000 each for BRCA1 and BRCA2 carriers where OC use was based on current use patterns. After the simulations, the "population" dataset was divided into ever and never users. Differences in outcomes were compared and 50,000 simulations were run for the general population and for BRCA1 and BRCA2 carriers.
2. *Age and duration analyses,* where sets of 20,000 simulations were run varying both age at first OC use (15, 20, 25, 30, 35, and 40 years) and duration of use (1, 2, 5, and 10 years). A total of 24 combinations were simulated (we did not model 10 years' duration starting at age 40). These simulations also indirectly captured the effect of recency of use on breast cancer since "recency" relative to age-specific breast cancer risk is a direct function of age at first use and duration of use.
3. *Two-dimensional simulations,* where individual values of the OC-associated relative risks were drawn from the distribution (n=200), followed by 10,000 simulations for each relative risk value, for a total of 2,000,000 simulations.

Modeled Outcomes

We used the model to estimate overall life expectancy and lifetime incidence and mortality from the five cancers and four acute vascular events; for the "direct" comparison of ever vs never users, we also estimated the absolute number of harms and benefits attributable to OC use per 100,000, and the number needed to harm or prevent (defined as 1 divided by the risk difference)

Sensitivity Analyses

We assessed the effect of uncertainty in the model structure and parameter values in several ways. First, for each set of simulations, we modeled the association between OC use and outcomes based on current use in two different ways: (1) where all cancer relative risks were based solely on ever versus never use and (2) where the risks for ovarian cancer were modeled on the basis of duration of use and the risks for breast cancer were modeled on ever vs never use and time since last use.

Second, we focused on age of starting use and duration of use by fixing the value of these across a wide range and then comparing the results. Third, we conducted a series of two-dimensional simulations, where the values for the relative risks of events were first drawn from the distributions described in Table 60, followed by a series of microsimulations, drawing "individual" values for BRCA status, race/ethnicity, and disease incidence and mortality from their appropriate distributions described in Table 61. For each outcome, we then generated the equivalent of "acceptability curves,"[371] where the proportion of sets of simulations where one strategy was "optimal" compared with another are illustrated at different thresholds for "optimality."

For outcome incidence and mortality, we used a net benefits approach.[371] In health economics, net monetary benefits (NMB) are defined as a function of willingness-to-pay (WTP) as follows:

NMB = (WTP * Effectiveness) – Costs

If WTP is measured in dollars per QALY, then NMB reduces to a single dollar figure. At any given WTP, the strategy with the highest NMB is preferred. Alternatively, the same approach can be applied using net health benefits (NHB):

NHB = (Costs/WTP) – Effectiveness

In a growing number of economic analyses, probabilistic analysis is used to estimate the effect of uncertainty in parameter values on the likelihood of making an optimal decision.[372] However, for those settings where costs are not explicitly being considered, this approach still has value. Harms can be considered "costs"—especially in the setting of preventive interventions.

For this analysis, we estimated separate harm/benefit ratios for incidence and mortality, with harms defined as the difference in incidence or mortality for breast and cervical cancer, and DVT, PE, MI, and stroke, and benefits as the difference in incidence or mortality for ovarian, colorectal, and endometrial cancers. For the incidence ratio, we varied the WTP from 0 net (no harms with some benefit) to 5.0 (5 extra incident cases for each case prevented) and benefits equivalent). For the mortality ratio, we varied the WTP from 0 (no excess mortality relative to deaths prevented) to 1.0 (excess mortality attributable to OC use exactly equivalent to prevented deaths attributable to OC use) We assumed that the harms and benefits compared here—all of which are associated with potential long-term morbidity and mortality—were roughly equivalent; obviously, this may not be the case, and appropriate weighting using validated preference measures is needed. Although this approach has been described,[373] it has not gained wide acceptance in the health economics literature. However, the simple comparison of net harms and benefits is frequently used in guidelines development,[374,375] and this approach may be particularly helpful in illustrating the effects of uncertainty on specific harms and benefits when developing practice or policy recommendations.

Results

Age-Specific Incidence of Relevant Outcomes With and Without OC Use

Estimated age-specific incidences of cancers among ever and never users of OCs are shown in Figures 41 to 45. At the ages of peak incidence, ever use is associated with an absolute reduction in ovarian cancer incidence of approximately 20 per 100,000 (Figure 41). For other cancers, peak incidence was increased by approximately 20 per 100,000 for breast cancer (Figure 42) and 4 per 100,000 for cervical cancer (Figure 43), and peak incidence decreased by approximately 50 per 100,000 for colorectal cancer (Figure 44) and 55 per 100,000 for endometrial cancer (Figure 45).

Figure 41. Estimated age-specific incidence of ovarian cancer among ever versus never OC users

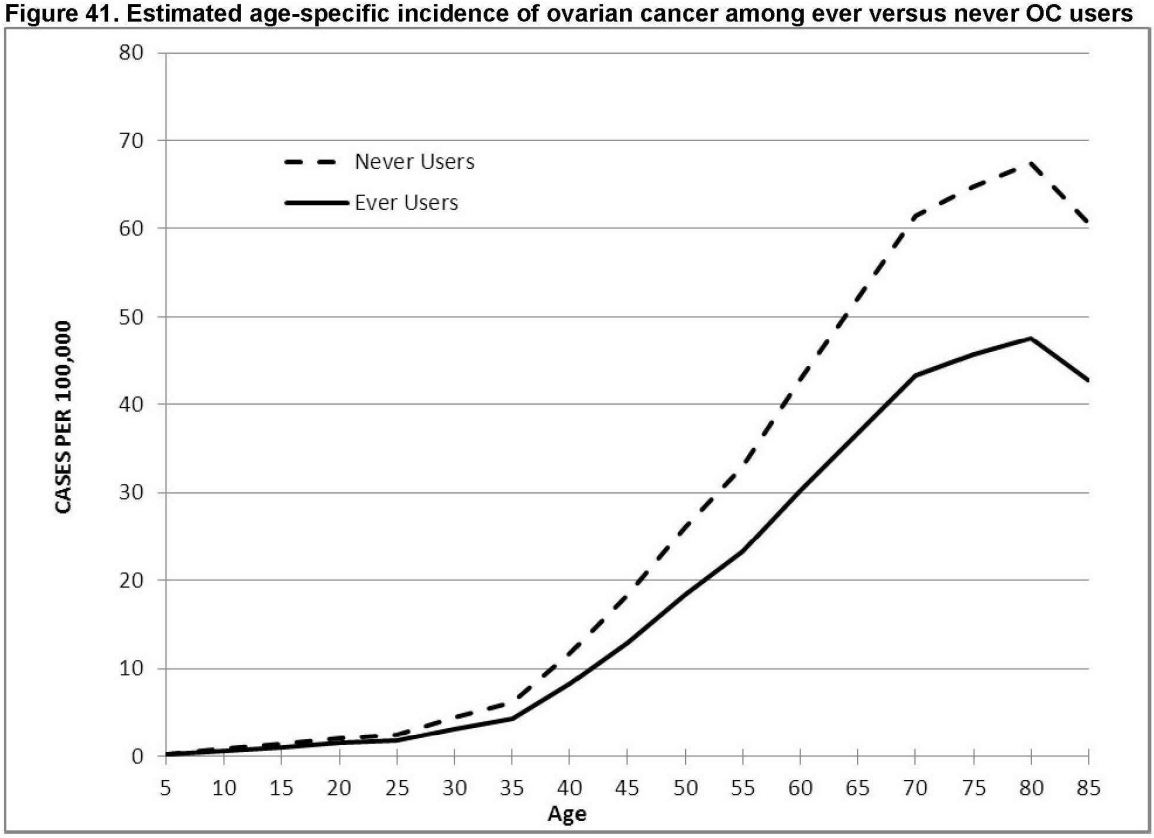


Figure 42. Estimated age-specific incidence of breast cancer among ever versus never OC users

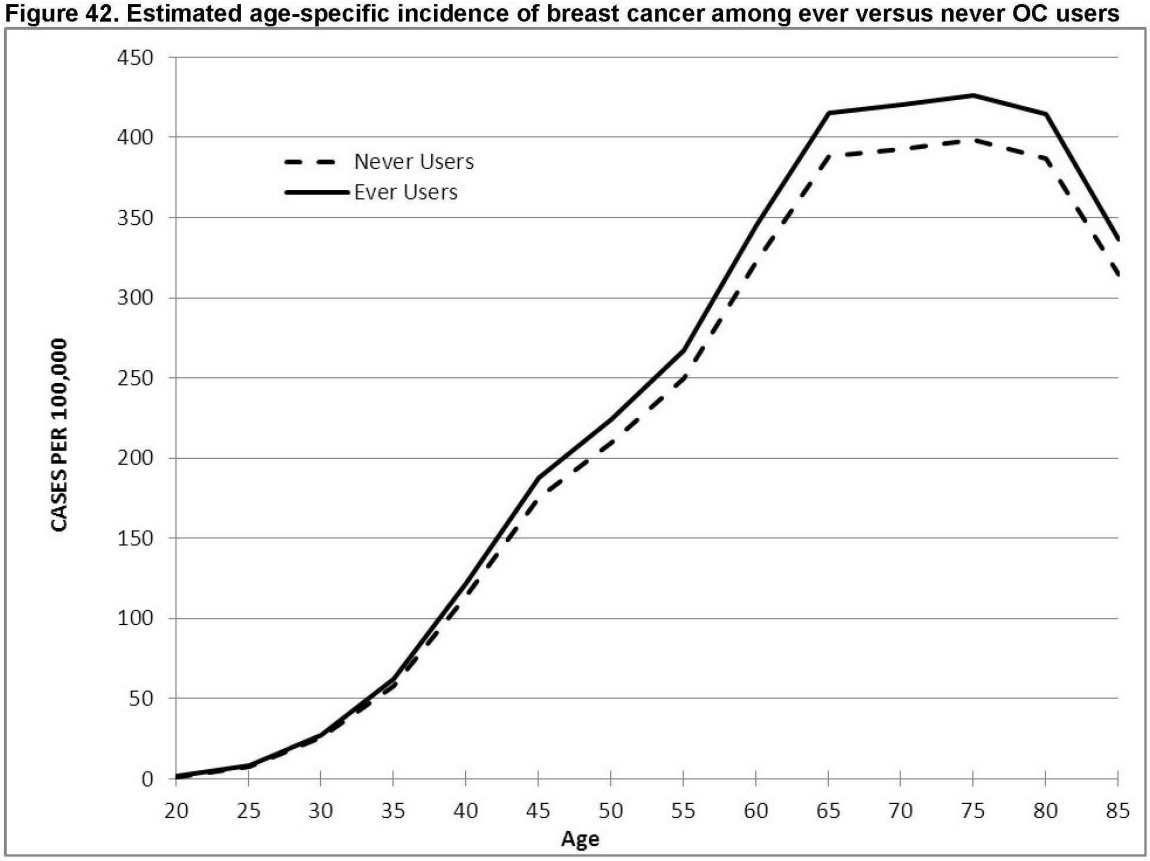


Figure 43. Estimated age-specific incidence of cervical cancer among ever versus never OC users

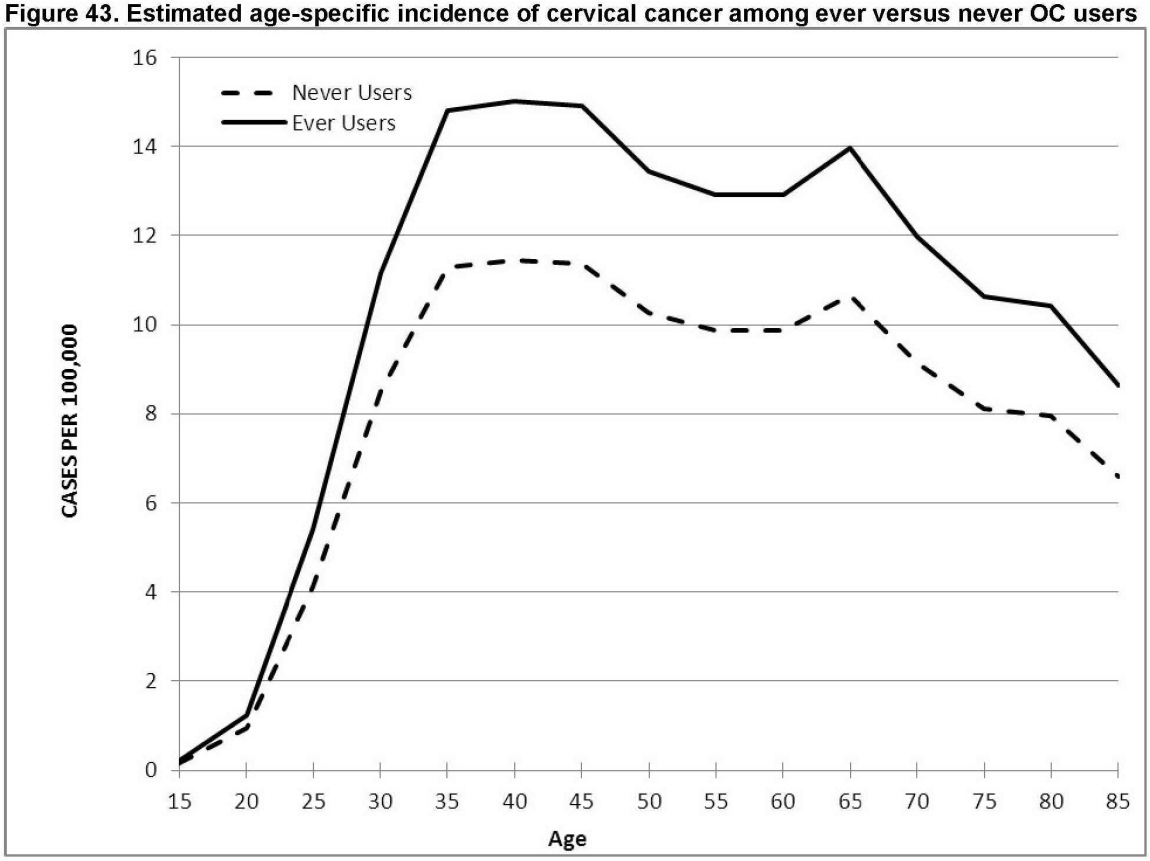


Figure 44. Estimated age-specific incidence of colorectal cancer among ever versus never OC users

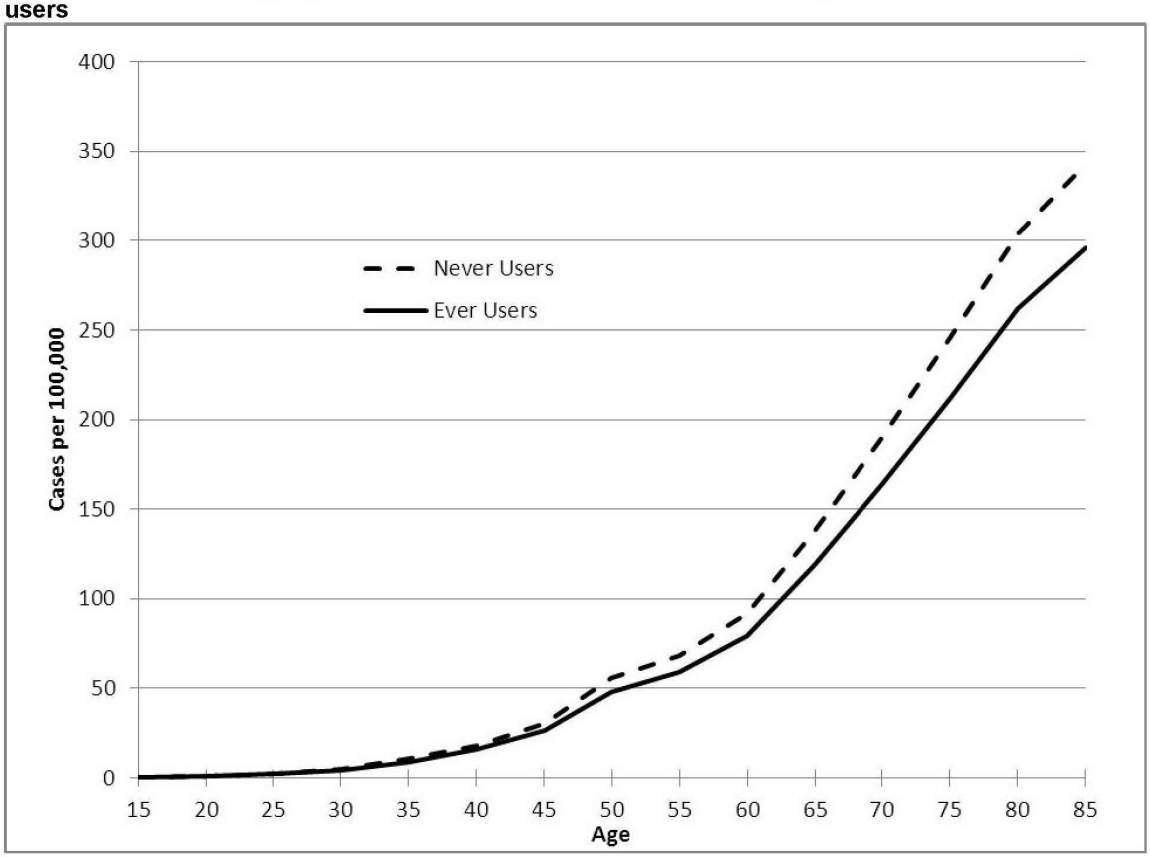
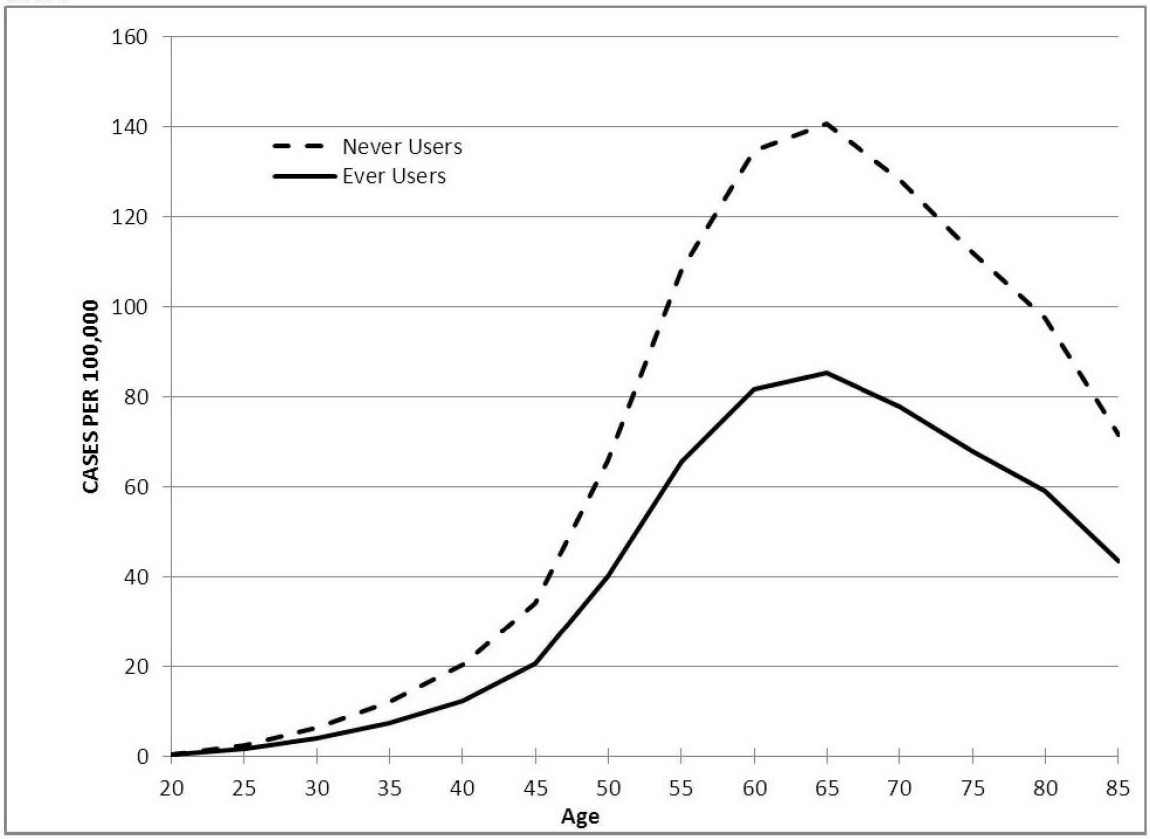


Figure 45. Estimated age-specific incidence of endometrial cancer among ever versus never OC users



Estimates for vascular events among current versus noncurrent users of OCs are shown in Figures 46 to 49. Peak increases in incidence were approximately 150 per 100,000 for DVT (Figure 46), 30 per 100,000 for PE (Figure 47), 30 per 100,000 for stroke (Figure 48), and 12 per 100,000 for acute MI (Figure 49); all of these were in women between the ages of 35 and 44. Note that the rates for all events merge at age 45. This is due to the lack of data on the prevalence of OC use in women over 45 years of age, since the best available data source, the NSFG, is limited to women aged 15 to 44. Because the formula for estimating incidence of an outcome based on exposure status subjects is derived from relative risk, overall incidence, and prevalence of exposure, there is no way to estimate the incidence in OC users over age 45, but it is certainly likely to be greater than for nonusers.

Figure 46. Estimated age-specific incidence of hospitalizations for deep vein thrombosis among current versus noncurrent OC users aged 15 to 44

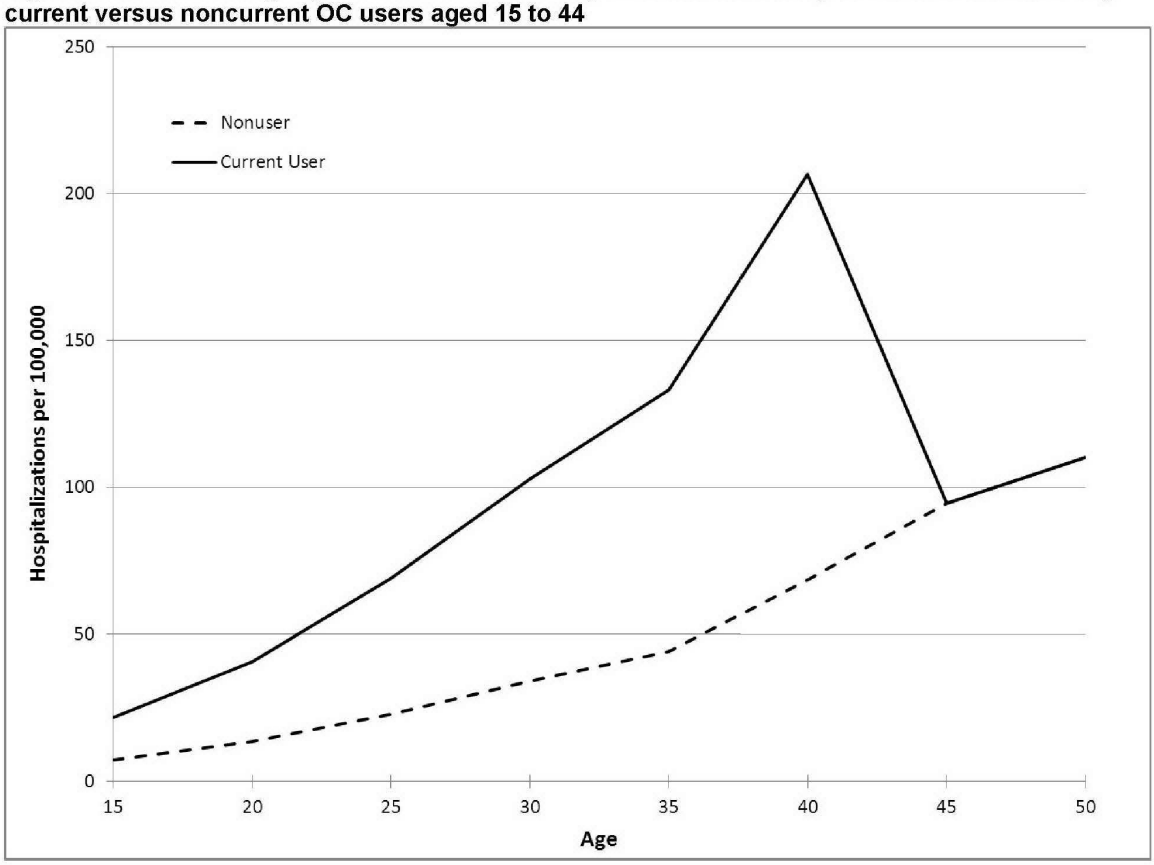


Figure 47. Estimated age-specific incidence of hospitalizations for pulmonary embolism among current versus noncurrent OC users aged 15 to 44

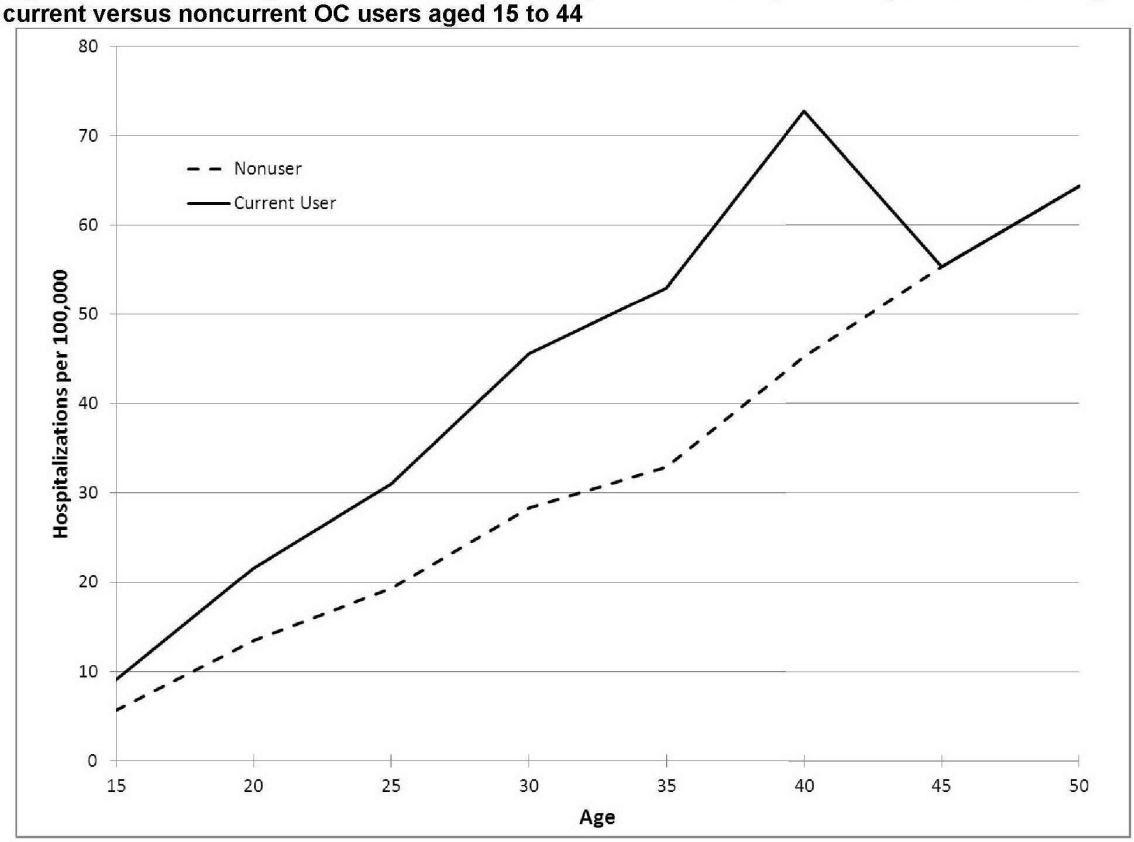


Figure 48. Estimated age-specific incidence of hospitalizations for stroke among current versus noncurrent OC users aged 15 to 44

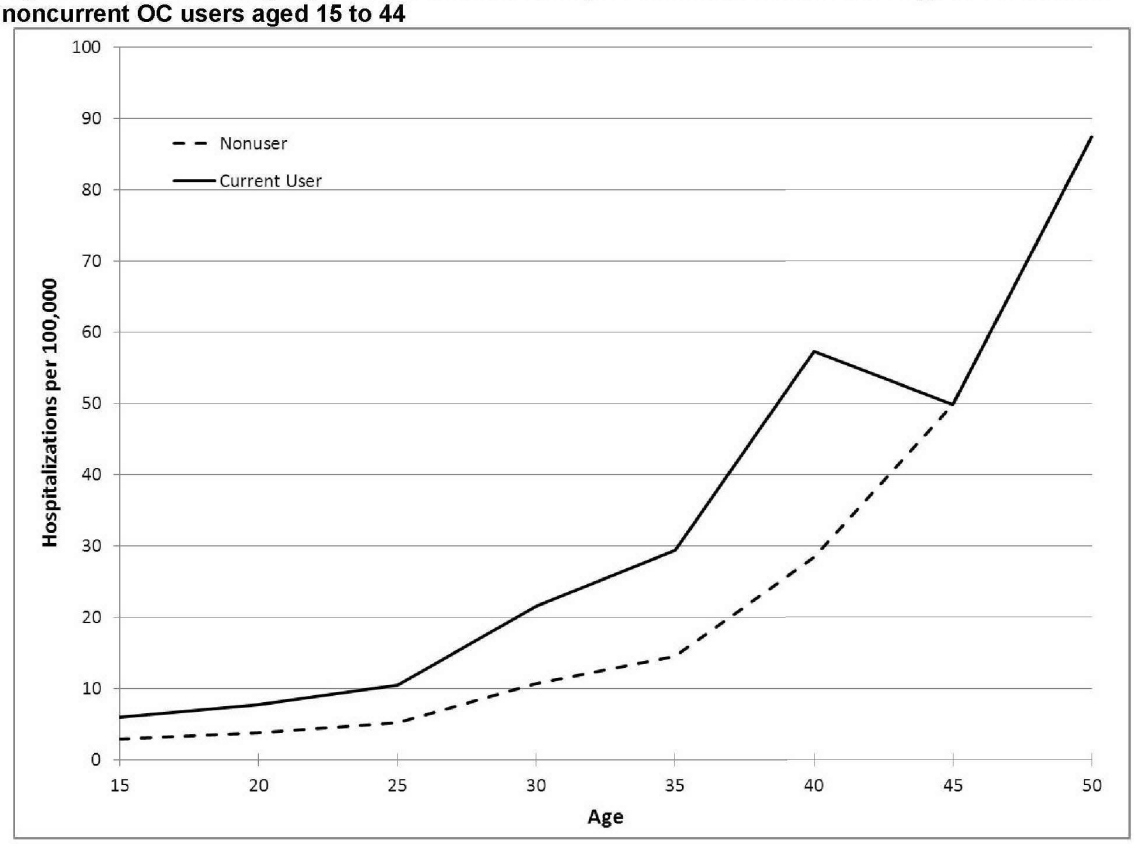


Figure 49. Estimated age-specific incidence of hospitalizations for acute myocardial infarction among current versus noncurrent OC users aged 15 to 44

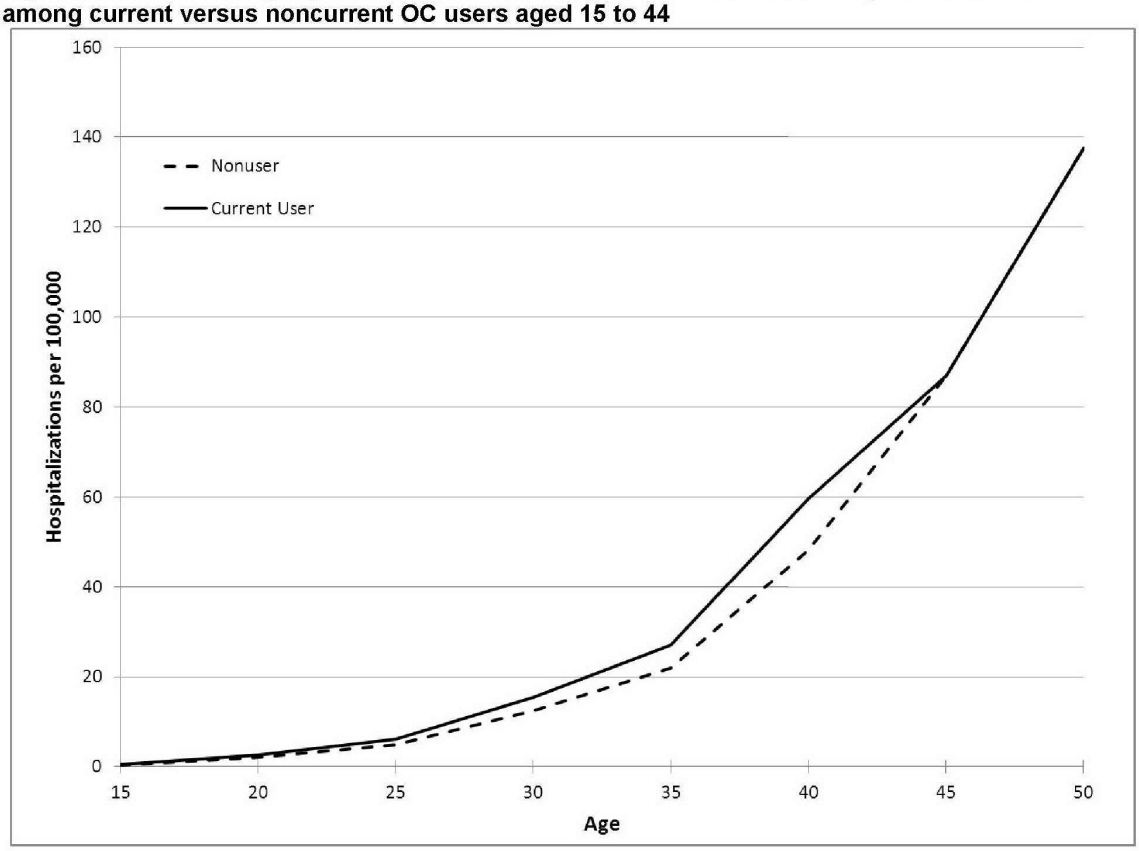


Figure 50 (for cancers) and Figure 51 (for vascular events) summarize the effects of OC use on age-specific incidence on a common scale. Each graph represents the estimated net difference in cases or hospitalizations per 100,000 in OC users compared with nonusers at each age. It is important to note that these estimates are for each individual outcome only and are not adjusted for competing risks such as hysterectomy or oophorectomy, or the occurrence of other outcomes, and effects of duration of use or time since last use are not incorporated.

Figure 50. Increase or decrease in age-specific incidence of cancers in ever OC users versus never users

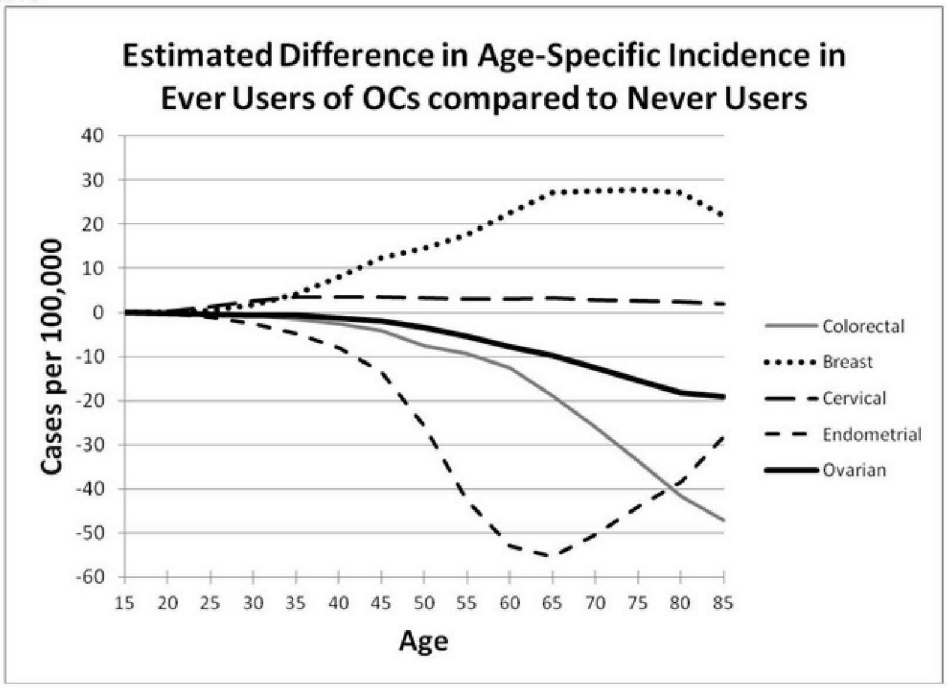
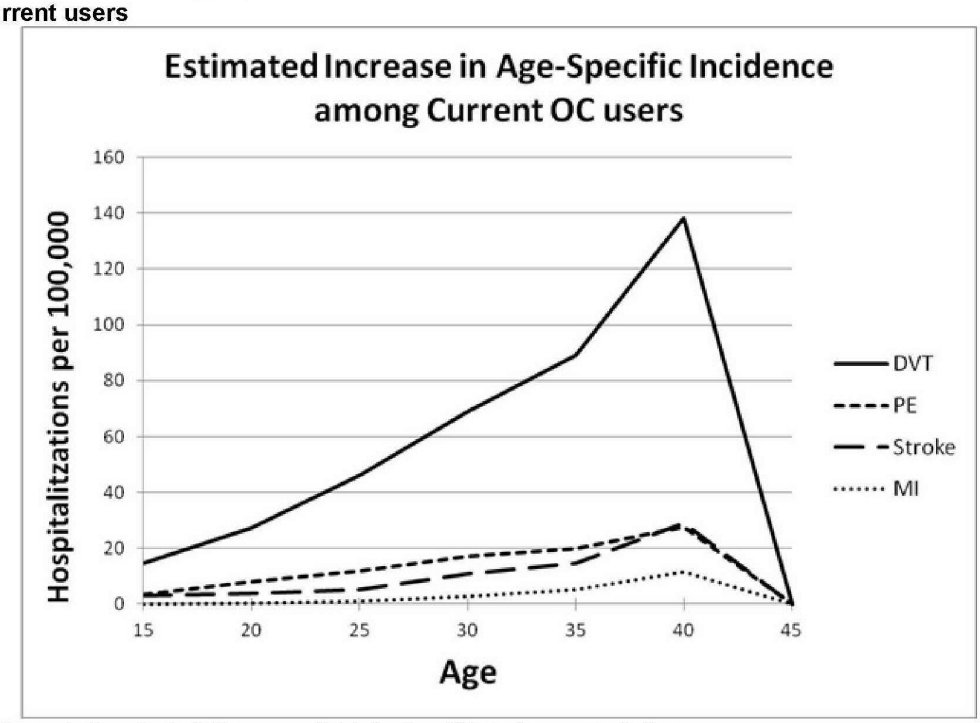


Figure 51. Increase in age-specific incidence of vascular events in current OC users versus noncurrent users



DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism

Effect of OC Use on Lifetime Incidence and Mortality

Table 63 shows the results of 60,000 simulations for the general population, along with 20,000 simulations each for BRCA1 and BRCA2 carriers; results were not qualitatively different by race or ethnicity. In this analysis, we estimate the overall effects of OC use based on current population patterns of use (including some women who never use OCs), and compare it to a simulated population that has the same patterns of pill us, but without any harms or benefits attributable to the pill (i.e., the risk of events in pill users is assumed to be identical to nonusers estimated base on relative risk estimates). Current patterns of OC use resulted in an increase in life expectancy of 1 to 2 months in the general population (with larger gains when modeled on the basis of duration), 10.5 months in BRCA1 carriers, and 1 month in BRCA2 carriers. Estimated ovarian cancer incidence and mortality, and overall mortality, in the model incorporating the joint effects of duration of use and time since last use was intermediate between estimates resulting from the ever/never and duration-only models. For clarity, we present only ever/never and duration only. Because there were no data on effects of duration of use or time since last use on outcomes in BRCA1 or BRCA2 carriers, effects of OCs were based on ever versus never use. Again, for the purposes of clarity, we omit confidence intervals but note that, even with this large number of simulations, the confidence intervals between different models overlapped.

Table 63. Estimated life expectancy and lifetime number of cases and deaths from cancers and vascular events

Outcome	All Women (n=60,000)			BRCA1 Only (n=20,000)		BRCA2 Only (n=20,000)	
	No Effect of OCs	OC-Attributable Effects		No Effect of OCs	OC- Attributable Effects	No Effect of OCs	OC- Attributable Effects
		Ever/ Never[a]	Time-Dependent[b]		Ever/ Never[a]		Ever/ Never[a]
Life expectancy	71.26	71.37	71.42	63.81	64.76	65.31	65.41
Lifetime Risks of Cancers							
Ovarian							
Developing	1.76%	1.42%	1.00%	48.92%	36.21%	14.15%	9.97%
Dying	0.99%	0.78%	0.55%	25.55%	19.33%	7.80%	5.63%
Breast							
Developing	10.52%	11.04%	11.14%	48.45%	54.09%	82.92%	85.89%
Dying	0.92%	0.98%	0.97%	5.11%	5.58%	8.14%	8.45%
Cervical							
Developing	0.54%	0.63%	0.60%	0.39%	0.61%	0.28%	0.47%
Dying	0.01%	0.01%	0.01%	0.00%	0.01%	0.00%	0.01%
Colorectal							
Developing	5.16%	4.70%	4.78%	3.42%	3.33%	3.44%	3.22%
Dying	1.72%	1.57%	1.64%	1.09%	1.05%	1.00%	1.03%
Endometrial							
Developing	3.21%	2.13%	2.15%	2.19%	1.63%	2.71%	1.50%
Dying	0.60%	0.41%	0.38%	0.42%	0.26%	0.52%	0.27%

Table 63. Estimated life expectancy and lifetime number of cases and deaths from cancers and vascular events (continued)

Outcome	All Women (n=60,000)			BRCA1 Only (n=20,000)		BRCA2 Only (n=20,000)	
	No Effect of OCs	OC-Attributable Effects		No Effect of OCs	OC- Attributable Effects	No Effect of OCs	OC- Attributable Effects
		Ever/ Never[a]	No Effect of OCs		Ever/ Never[a]		Ever/ Never[a]
Life expectancy	71.26	71.37	71.42	63.81	64.76	65.31	65.41
Lifetime Risks of Other Outcomes							
DVT							
Cases	8.54%	8.74%	8.77%	5.77%	6.30%	5.79%	5.47%
Deaths	0.45%	0.50%	0.50%	0.34%	0.38%	0.40%	0.34%
PE							
Cases	4.89%	4.89%	4.89%	3.46%	3.19%	3.13%	3.14%
Deaths	0.43%	0.40%	0.39%	0.27%	0.29%	0.27%	0.23%
Stroke							
Cases	10.53%	10.38%	10.36%	7.31%	7.44%	6.26%	6.45%
Deaths	0.87%	0.79%	0.79%	0.48%	0.58%	0.53%	0.48%
MI							
Cases	15.62%	15.66%	15.68%	11.10%	11.27%	9.02%	9.42%
Deaths	1.99%	1.98%	2.01%	1.48%	1.51%	1.07%	1.04%

BRCA = breast cancer genetic mutation; DVT = deep venous thrombosis; MI = acute myocardial infarction; OC = oral contraceptive; PE = pulmonary embolism

[a]Association between OC use and ovarian and breast cancers modeled as ever versus never users.

[b]Association between OC use and ovarian cancer dependent on duration of use, and between OC use and breast cancer on time since last use.

This gain was largely attributable to decreases in ovarian cancer (which, while uncommon, has a high mortality rate), and colorectal cancer, which is common and has an intermediate mortality rate. While OC use did increase breast cancer cases, the relative increase in mortality from breast cancer was lower than the decrease from ovarian and colorectal cancer. This outcome is likely due to two factors. First, the overall case mortality rate for breast cancer is lower than for ovarian or colorectal cancer, even without adjusting for any effect of OCs on mortality through screening and/or biological changes. Second, by increasing age-specific incidence, cases are diagnosed at an earlier age—because we used age-specific survival in the model, this will lead to lower expected mortality. Finally, we assumed that 5-year survivors were no longer at risk for cancer death (although breast cancer survivors were at risk for a contralateral new cancer), which may also be contributing to lower overall mortality (other than BRCA carriers, who were at increased risk for both breast and ovarian cancers, we assumed the risk of different cancers was independent—women with a history of breast cancer were as likely to develop ovarian or other cancers as women who did not). The effect on mortality of cases occurring at younger ages is also seen for vascular events; in some iterations of the model, mortality was even reduced among users compared with nonusers, although some of this is also because of the large variance around the probability estimates due to the small number of cases. The prevalence of ever use in the models averaged approximately 75 percent across all iterations, which is somewhat lower than the 84 percent reported in the NSFG. However, given the relative magnitudes of the different effects, this likely leads to underestimation of overall net benefit.

The relative effects of incidence and disease-specific mortality are particularly clear in the results for BRCA1 and BRCA2 carriers. For BRCA1 carriers—where the relative increases in risk of breast and ovarian cancer are similar and result in similar lifetime risks of close to 50

percent in this model—the absolute reduction in ovarian cancer mortality is approximately 6 percent, while the absolute increase in breast cancer mortality is less than 1 percent, resulting in a gain in life expectancy of over 10 months. Conversely, for BRCA2 carriers—where the increased risk of breast cancer is much larger than for ovarian cancer (83% vs. 14%)—resulted in a smaller absolute reduction in mortality. The estimated number of other cancers and vascular events is also smaller for the BRCA carriers, largely due to the large competing risks associated with breast and ovarian cancers. As with the general population, the combination of small probabilities and earlier diagnosis lead to some paradoxical results in terms of the effect of OC use on incidence and mortality.

These results reflect estimates of the population-level impact of associations between OC use and these outcomes based on current patterns of OC use—in other words, the weighted average based on estimates of the population distribution of ever use, age at first use, and duration of use. Because the "OC use" model includes "subjects" who never use OCs, the absolute difference in outcomes at the population level will be lower than it will be when directly comparing ever users to never users.

Effect of OC Use on Lifetime Incidence and Mortality in Ever Versus Never Users

To estimate absolute differences in outcomes between ever users and never users, we generated a "population" of women who had used OCs based on reported patterns, then calculated life expectancy and incidence and mortality from cancers and vascular events for "subjects" who had "taken" OCs during the simulation versus those who had not. We performed 50,000 iterations for the general population and 20,000 each for BRCA1 and BRCA2 carriers.

In Table 64, the estimated life expectancy and lifetime number of cases and deaths from cancers and vascular events is compared between ever versus never users. The results are qualitatively similar but somewhat larger in scale than seen when modeled as a general population effect, where the effect is the weighted average of incidence in users and nonusers. Estimated gains in life expectancy ranged from 5 months for BRCA2 carriers to 11.5 to 12.5 months for the general population, to 16 months for BRCA1 carriers. The incidence estimates for never users are also somewhat higher than in the population model, which is likely due to differences resulting from the effect of actually modeling no use, which may slightly modify the effects of differences in possible state transition compared with the general population model, which assumes similar patterns of pill use but no pill effects on cancers or vascular events.

Table 64 presents these results as the absolute number of case or deaths caused or prevented by OC use per 100,000 women over a lifetime starting at age 10. We also present the number needed to harm (NNH) or number need to prevent (NNP), which is the reciprocal of the absolute risk associated with OC use. For the general population, modeling the effects of exposure as time-dependent compared with ever vs never has an impact on the magnitude of the effect of OC use on both harms and benefits, increasing the number of breast cancer cases but decreasing the number of ovarian cancer. Although the qualitative effects are similar, and the absolute difference between the two different modeling approaches is quite small, the fact that they are different illustrates the potential importance of better data about the relationship between duration of use, time since last use, and the risk of developing specific cancers. There are also some paradoxical results for BRCA carriers (for example, decreased incidence but increased mortality for colorectal cancer among both BRCA1 and BRCA2 carriers), but it is unclear whether this represents the instability of relatively small numbers, or perhaps a competing risk

effect because of the high background risk of mortality from ovarian cancer which is reduced by OC use. This series of simulations also resulted in lower estimated mortality, despite increased incidence, from breast cancer when OC effects are modeled based on time or in BRCA1 carriers. As noted in the meta-analysis, breast cancer incidence is increased by OC use, but mortality was not significantly increased. These model results, which are based only on modeling an increased incidence, suggest that some of the effect observed in the studies may be the result of shifts in age-specific incidence resulting in better overall survival. As noted below, we observed similar effects for stroke, which are almost entirely explained by differences in age distribution of cases. Some of this may also be related to a relatively small number of "subjects" with no history of OC use in the simulated data set. Finally, there are structural differences in competing risks depending on how the effects of OC use on the outcomes considered here are modeled, which may also contribute to this effect.

Table 64. Estimated lifetime excess cases and deaths (harms) and prevented cases (benefits) per 100,000 women

Outcome	General Population				BRCA1		BRCA2	
	Ever/Never[a]		Duration[b]					
	Excess (Prevented) per 100,000	Number Needed To Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed To Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed To Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed To Harm (Prevent)
Harms								
Breast Cancer								
Cases	1021	98	(345)	(290)	2080	48	2268	44
Deaths	(170)	(588)	(263)	(380)	(48)	(2078)	318	315
Cervical Cancer								
Cases	7	14154	74	1356	149	671	217	461
Deaths	0	4513455	11	9369	7	14899	7	15029
DVT								
Cases	1226	82	1277	78	1059	94	45	2215
Deaths	4	24208	20	4959	46	2184	(77)	(1297)
PE								
Cases	524	191	530	189	575	174	451	222
Deaths	484	207	468	214	432	232	317	315
Stroke								
Cases	1329	75	1177	85	1819	55	1461	68
Deaths	77	1300	37	2706	138	726	(105)	(949)
MI								
Cases	1253	80	1645	61	1823	55	1396	72
Deaths	378	264	448	223	(33)	(3009)	149	671
Total harms								
Cases	5361	19	4357	23	7505	13	5840	17
Deaths	773	129	720	139	541	185	608	164
Benefits								
Ovarian cancer								
Cases	(806)	(124)	(1076)	(93)	(9701)	(10)	(4300)	(23)
Deaths	(389)	(257)	(566)	(177)	(4478)	(22)	(1845)	(54)
Colorectal Cancer								
Cases	(802)	(125)	(717)	(139)	(810)	(123)	(682)	(147)
Deaths	(374)	(267)	(321)	(312)	50	2017	49	2021
Endometrial Cancer								
Cases	(1344)	(74)	(1421)	(70)	(1553)	(64)	(1996)	(50)
Deaths	(145)	(690)	(160)	(625)	(71)	(1402)	(85)	(1181)

Table 64. Estimated lifetime excess cases and deaths (harms) and prevented cases (benefits) per 100,000 women (continued)

Outcome	General Population				BRCA1		BRCA2	
	Ever/Never[a]		Duration[b]					
	Excess (Prevented) per 100,000	Number Needed to Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed to Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed to Harm (Prevent)	Excess (Prevented) per 100,000	Number Needed to Harm (Prevent)
Total Benefits								
Cases	(2952)	(34)	(3215)	(31)	(12064)	(8)	(6978)	(14)
Deaths	(908)	(110)	(1046)	(96)	(4500)	(22)	(1880)	(53)

BRCA = breast cancer genetic mutation; DVT = deep venous thrombosis; MI = acute myocardial infarction; OC = oral contraceptive; PE = pulmonary embolism

[a]Association between OC use and ovarian and breast cancers modeled as ever versus never users.

[b]Association between OC use and ovarian cancer dependent on duration of use, and between OC use and breast cancer on time since last use.

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Effect of Age at First Use and Duration of OC Use

Figures 52 to 76 present the results of simulations at varying ages of starting OCs (15, 20, 25, 30, 35, and 40 years) and duration of use (1, 2, 5, and 10 years) for cancer incidence and mortality, vascular event incidence and mortality, overall life expectancy and combined benefits and harms, and harm to benefit ratio. For all except life expectancy and the harm/benefit ratios, results are presented as changes in absolute incidence or mortality relative to no OC use—values above 0 reflect an increase relative to no OC use, while values below 0 reflect a decrease relative to OC use. Life expectancy is presented as absolute difference in fractions of years. For the harm/benefit ratio, values less than 0 indicate that total harms are reduced relative to no use; values between 0 and 1 indicate that harms are increased but that benefits exceed harms; and values greater than 1 indicate that harms exceed benefits.

Not surprisingly, the relationship between duration of use and outcome is strongest for ovarian cancer, since the effect of OC use on ovarian cancer incidence is directly modeled as a function of duration. There may be an interaction between age at first use and duration for breast cancer. The effect of OC use on breast cancer is modeled as a constant risk until stopping, with a subsequent decline over time. Therefore, women who start at later ages for longer periods of time may be at greater risk because breast cancer incidence increases with age. However, the results of the simulations do not show a clear relationship between age at first use and duration, which may be a function of the relatively small number of simulations for each age/duration combination. There do not appear to be any age/duration effects for the remaining cancers (again, likely due to exposure being modeled simply as ever vs. never use).

For vascular events, there was no clear relationship between age at first use and risk, but estimates for incidence and mortality tended to converge at 10 years of use for all ages of first use. This likely due to the assumption of constant risk—at longer durations of use, there is more opportunity for any effect of OC use on the event to occur, and the estimates are more stable.

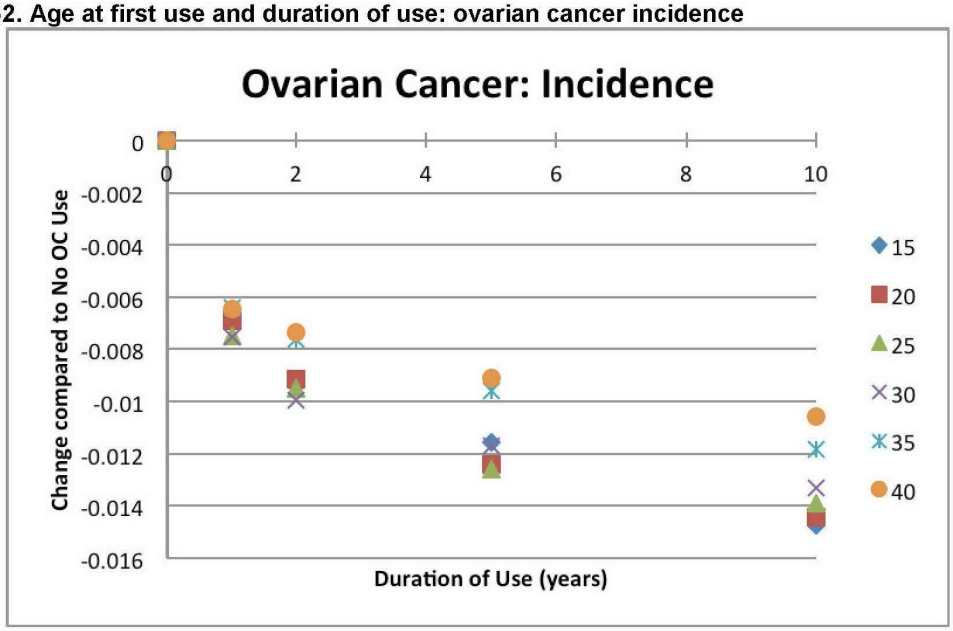
For several of the outcomes, particularly breast cancer and stroke, overall lifetime incidence is decreased but overall lifetime cause-specific mortality is decreased for some groups, even though we do not model a separate effect of OC use on cause-specific mortality. There are several possible explanations for this, including random “noise” for rare events, the effects of competing risks, and structural factors in the model (for example, although “women” remain at risk for subsequent events such as a second VTE, this probability is not conditioned on experiencing a previous VTE while on OCs). However, some of the reductions in cause specific mortality may also be related to changes in age-specific mortality from specific conditions—increasing age-specific incidence while on OCs will by definition lead to a shift in the overall incidence to younger ages. Because survival after diagnosis for these conditions is better for younger women (because of lower prevalence of comorbid diseases and, in the case of cancers, potential shifts in stage distribution because of screening), it is possible to have increased incidence along with decreased mortality. We tested this hypothesis for stroke by fixing in-hospital stroke mortality in the model to the national average (9.8%) rather than to age-specific values, which vary from 7.8% in women under 45 years of age to 12.8% in women 85 years and older. Lifetime stroke mortality was 0.9 percent for no OC use, 0.83 percent when modeled as age-specific mortality, and 1.1 percent when modeled at the fixed overall rate, demonstrating the effect of changes in age-specific incidence on overall mortality if mortality is variable across age.

Similar convergences with longer duration of use were observed for combined harms and benefits, with an overall greater reduction in mortality from ovarian, colorectal, and endometrial cancer compared with the increased mortality from other causes (note that the trend was not perfect, which may be due to unstable estimates resulting from too few simulations).

Use of OCs for 5 years or less was associated with net increase in life expectancy except for women 35 years and older. Longer durations were associated with gains in life expectancy in younger women but not women 30 years and older. This is largely explained by the impact of deaths occurring at younger age on overall life expectancy—more potential years lost has a greater impact. These results are consistent with the results showing net gains in life expectancy in Tables 63 and 64: if, as the age of first use versus duration effects suggest, net benefit is optimized by 5 years of use, then one would expect net increases in life expectancy in a population that has a mean duration of use of 5 years, which is the value used in the model.

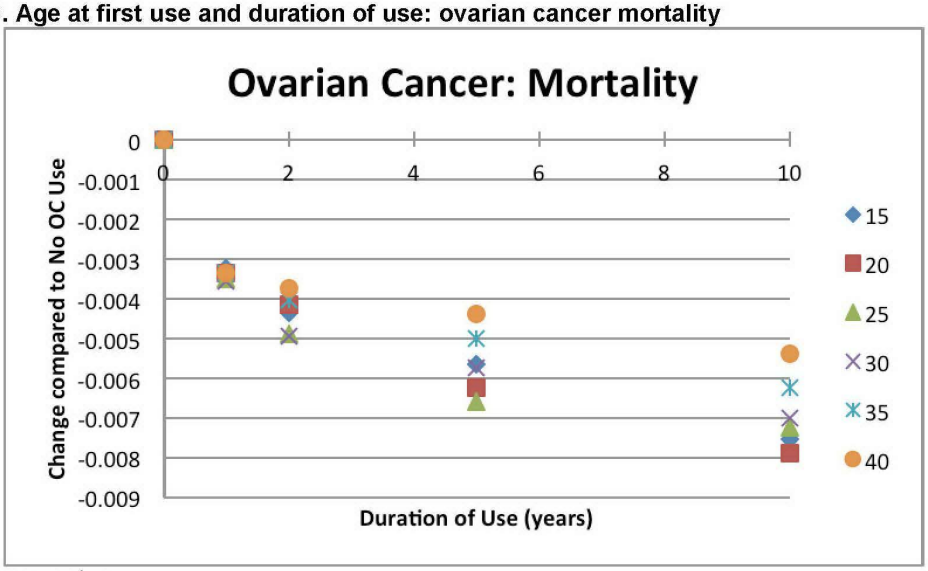
Note that for each figure, the different shapes 15, 20, 25, 30, 35, and 40 represent the age of starting OC use, while the y-axis represents the absolute change in lifetime incidence or mortality due to the estimated association between OC use and the outcome.

Figure 52. Age at first use and duration of use: ovarian cancer incidence



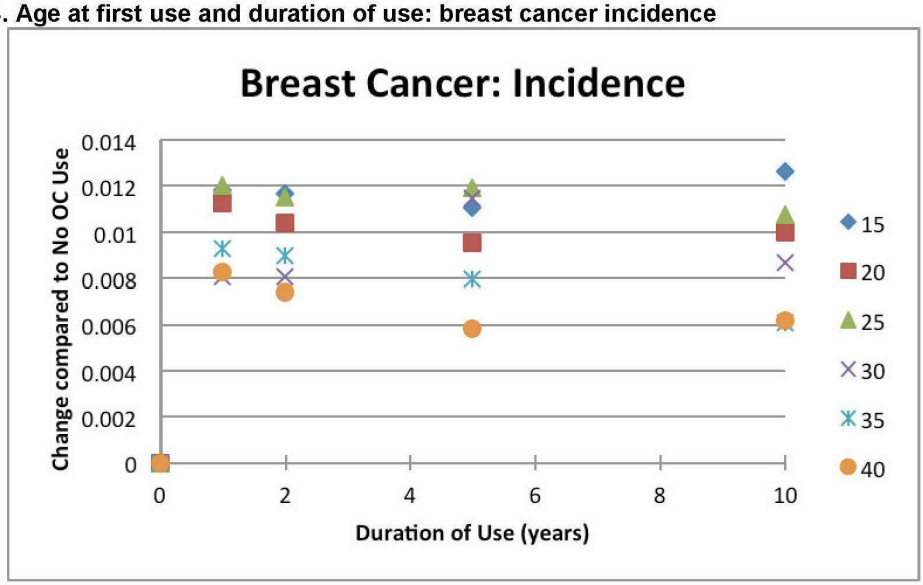
OC = oral contraceptive

Figure 53. Age at first use and duration of use: ovarian cancer mortality



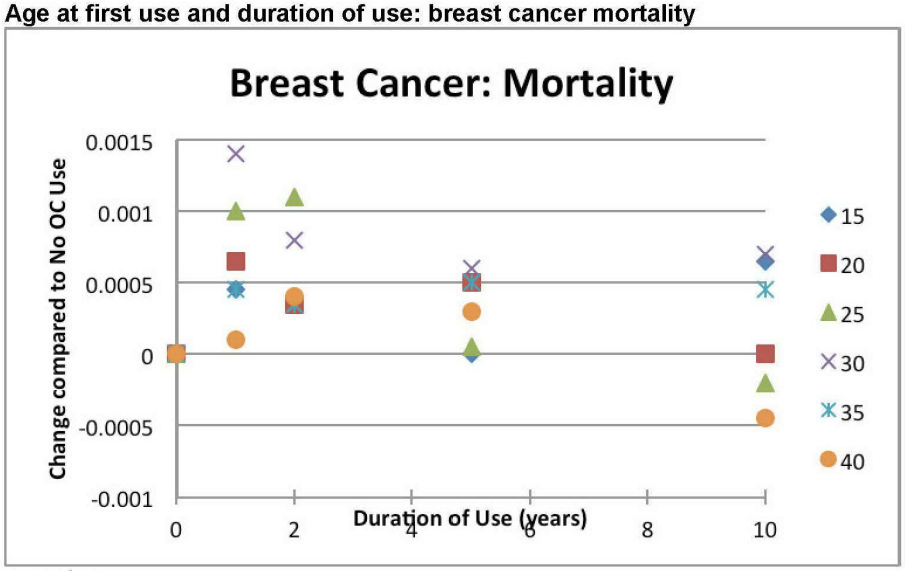
OC = oral contraceptive

Figure 54. Age at first use and duration of use: breast cancer incidence



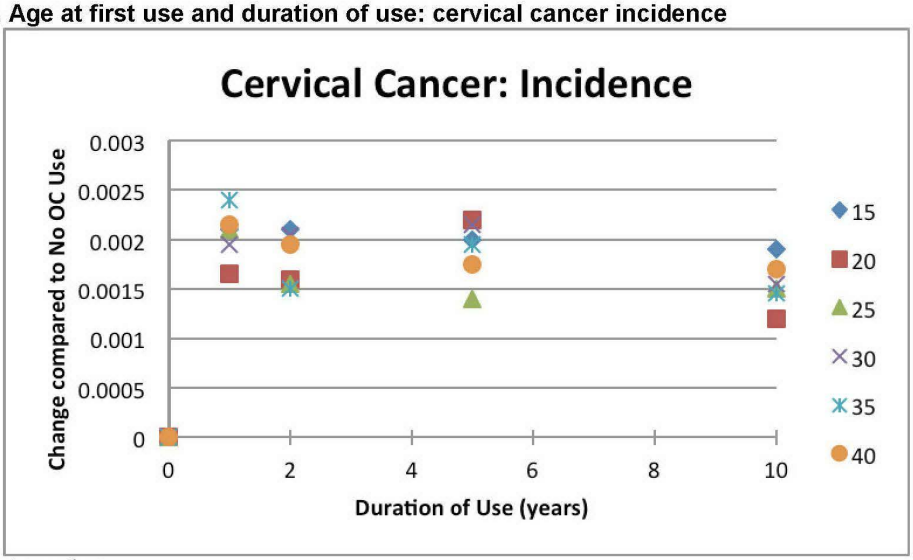
OC = oral contraceptive

Figure 55. Age at first use and duration of use: breast cancer mortality



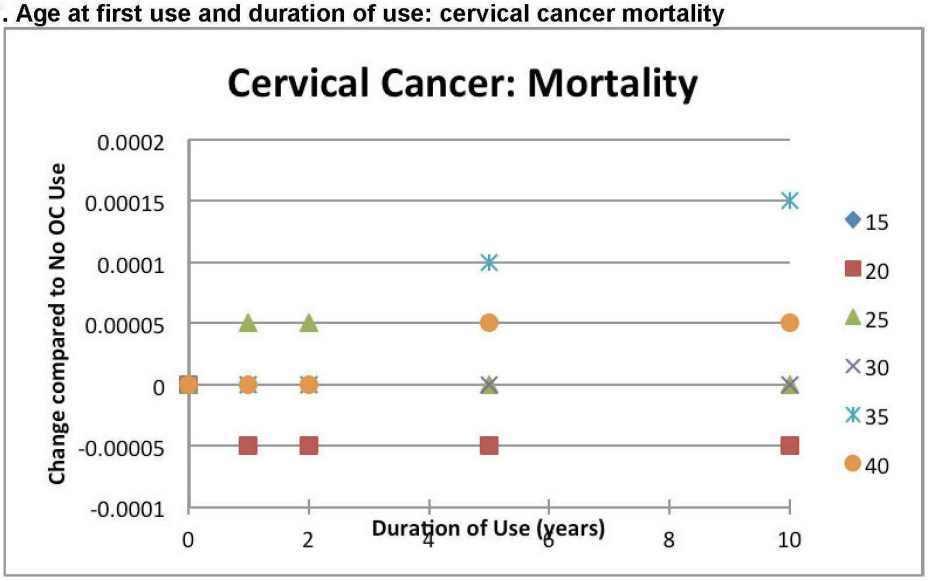
OC = oral contraceptive

Figure 56. Age at first use and duration of use: cervical cancer incidence



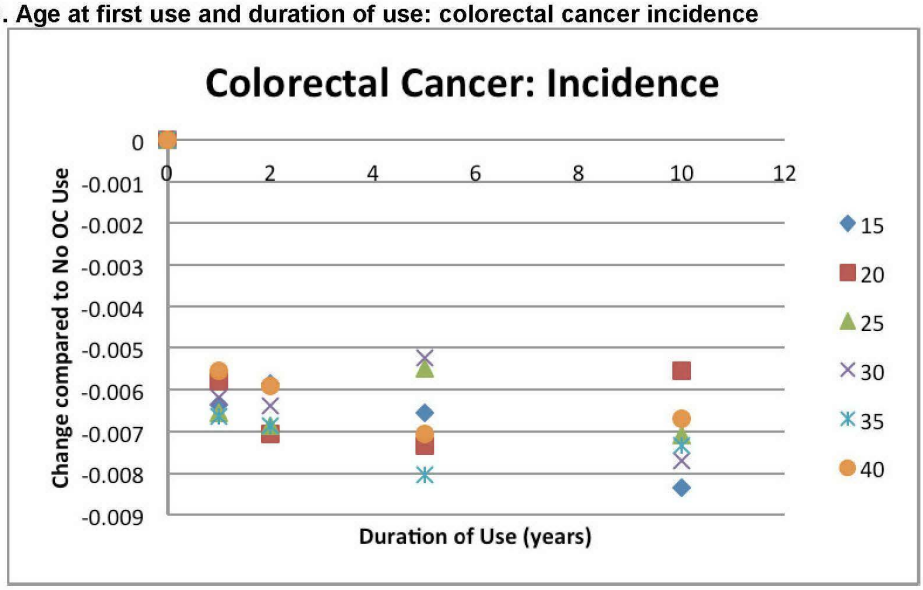
OC = oral contraceptive

Figure 57. Age at first use and duration of use: cervical cancer mortality



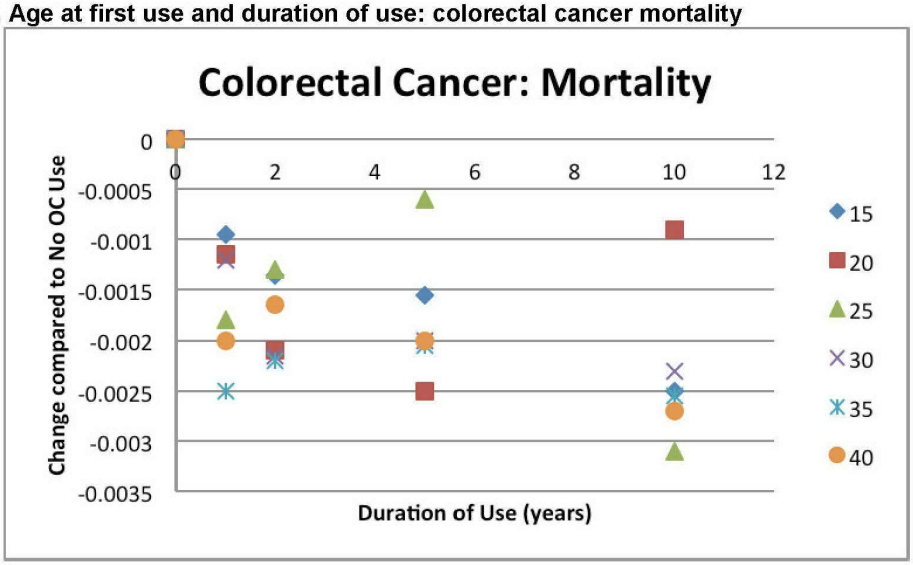
OC = oral contraceptive

Figure 58. Age at first use and duration of use: colorectal cancer incidence



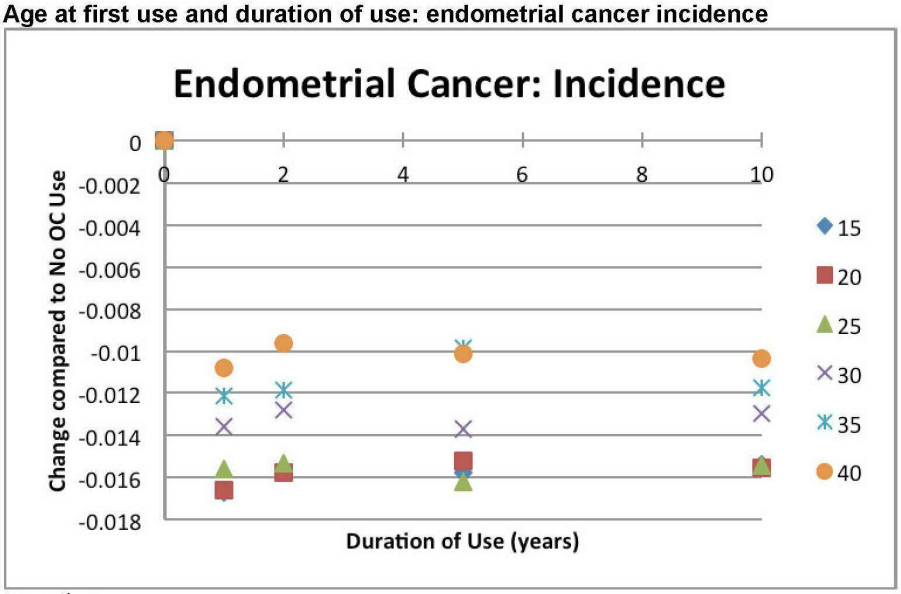
OC = oral contraceptive

Figure 59. Age at first use and duration of use: colorectal cancer mortality



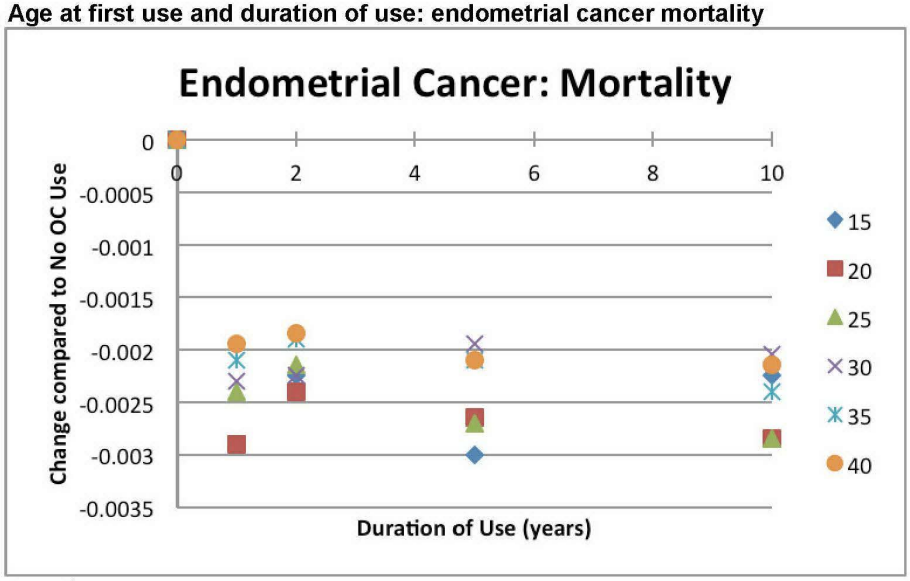
OC = oral contraceptive

Figure 60. Age at first use and duration of use: endometrial cancer incidence



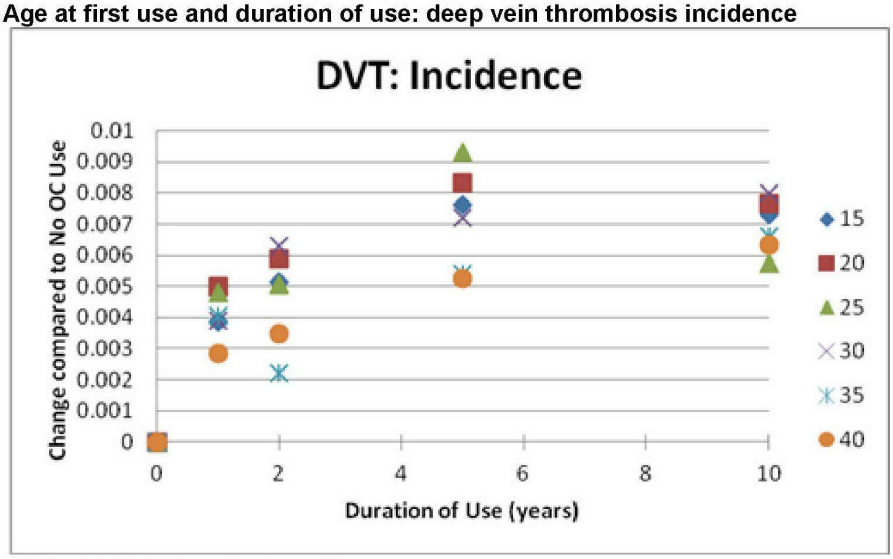
OC = oral contraceptive

Figure 61. Age at first use and duration of use: endometrial cancer mortality



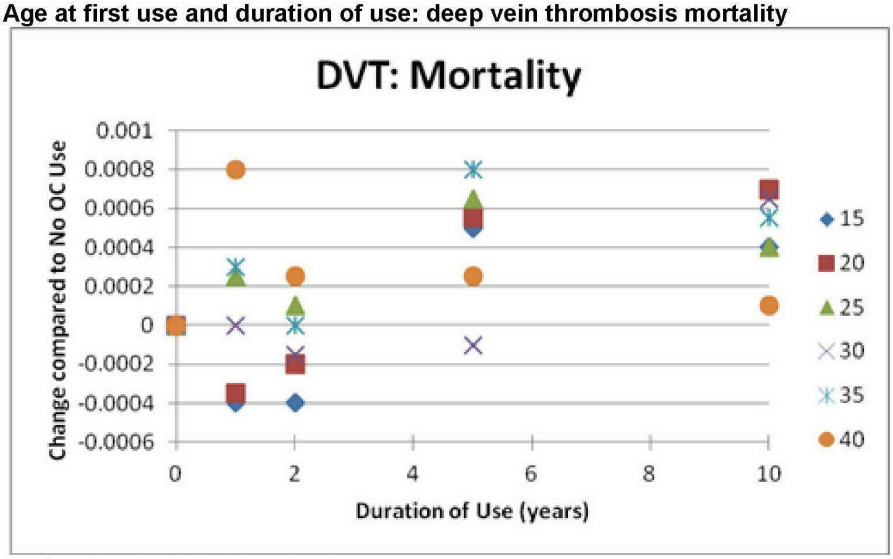
OC = oral contraceptive

Figure 62. Age at first use and duration of use: deep vein thrombosis incidence



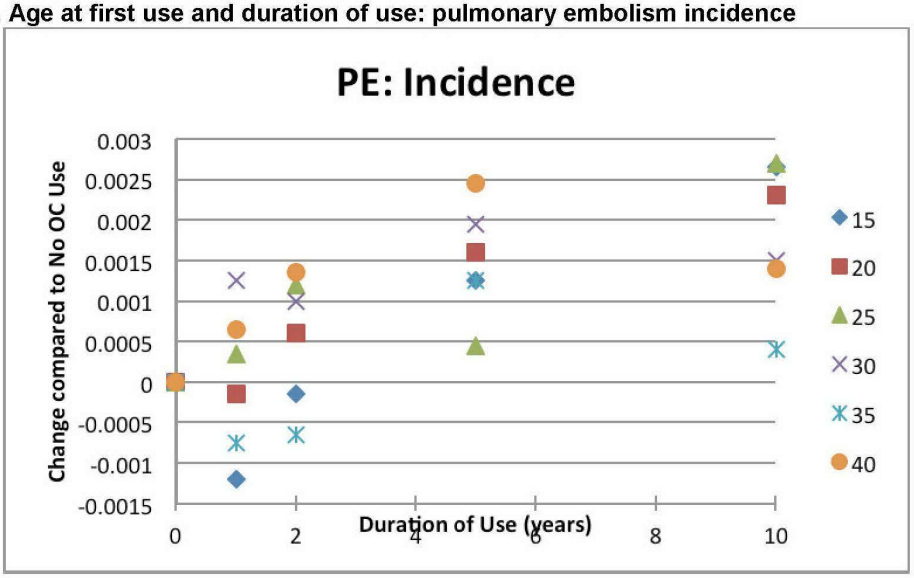
DVT = deep vein thrombosis; OC = oral contraceptive

Figure 63. Age at first use and duration of use: deep vein thrombosis mortality



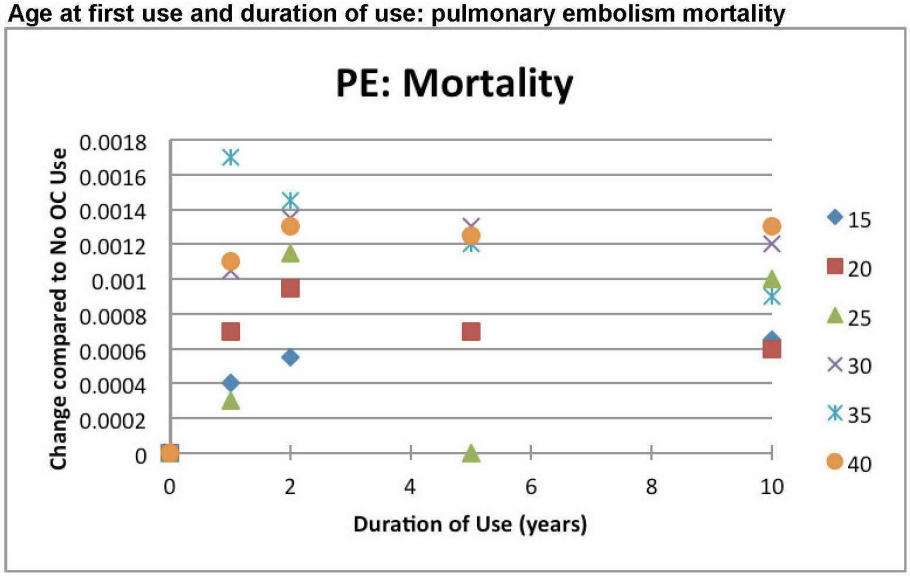
DVT = deep vein thrombosis; OC = oral contraceptive

Figure 64. Age at first use and duration of use: pulmonary embolism incidence



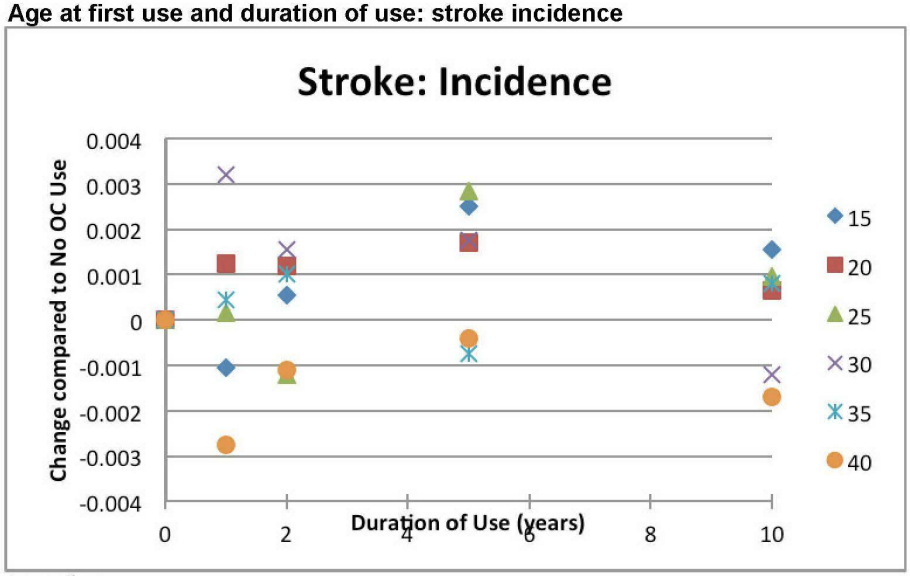
OC = oral contraceptive; PE = pulmonary embolism

Figure 65. Age at first use and duration of use: pulmonary embolism mortality



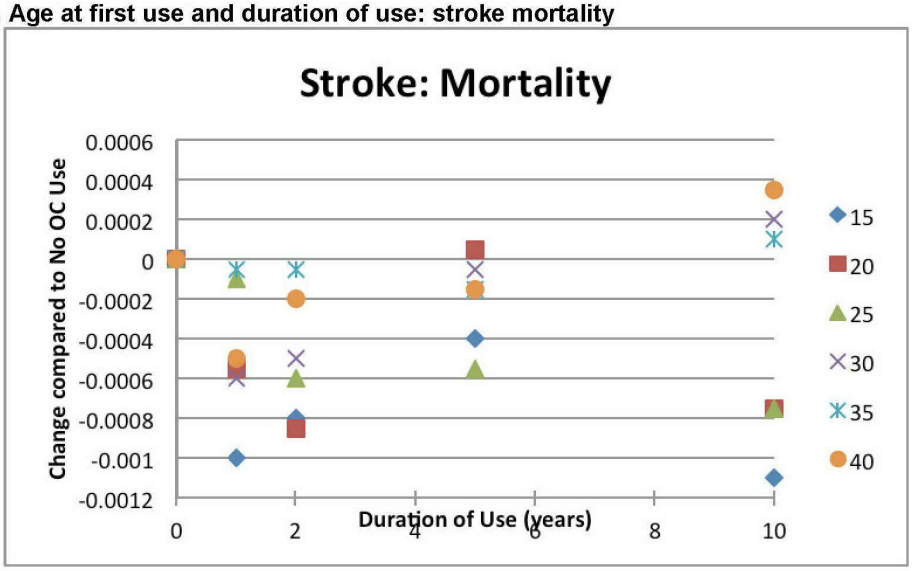
OC = oral contraceptive; PE = pulmonary embolism

Figure 66. Age at first use and duration of use: stroke incidence



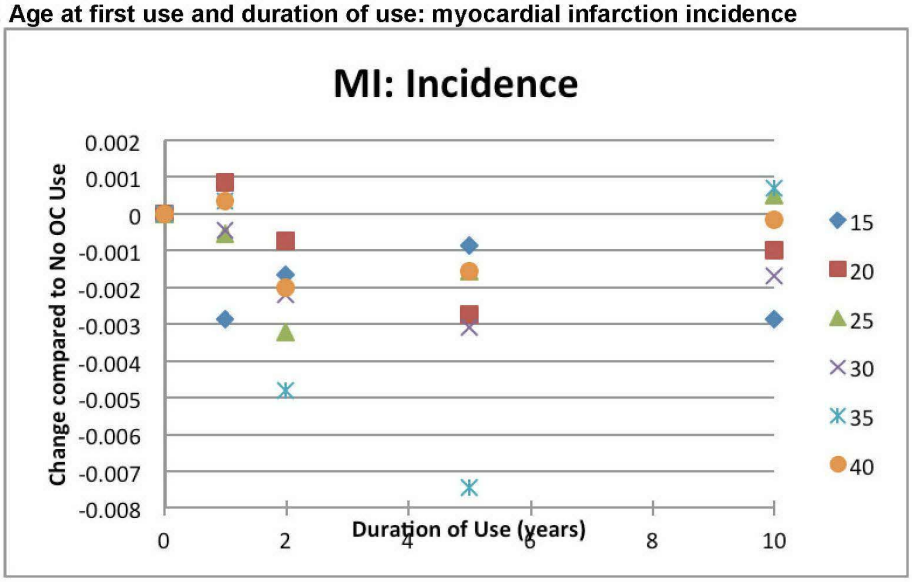
OC = oral contraceptive

Figure 67. Age at first use and duration of use: stroke mortality



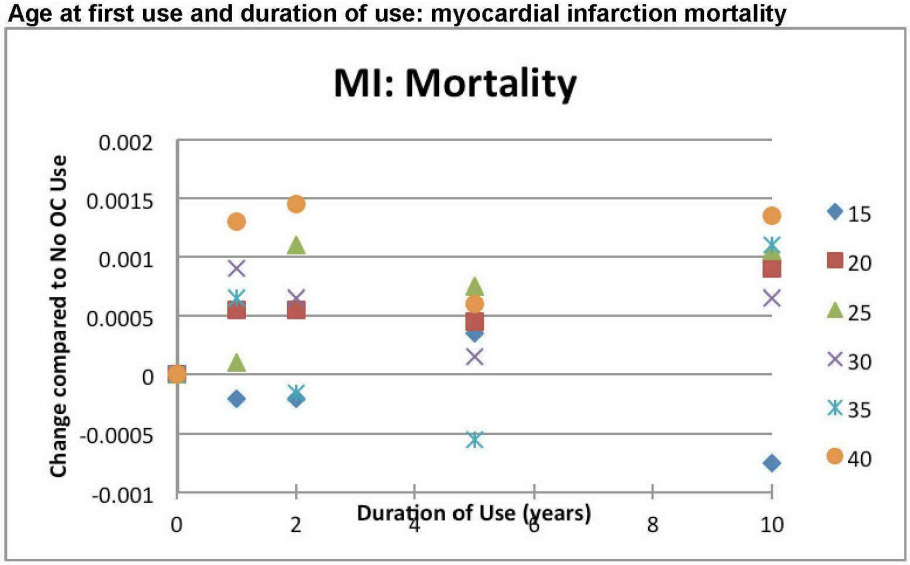
OC = oral contraceptive

Figure 68. Age at first use and duration of use: myocardial infarction incidence



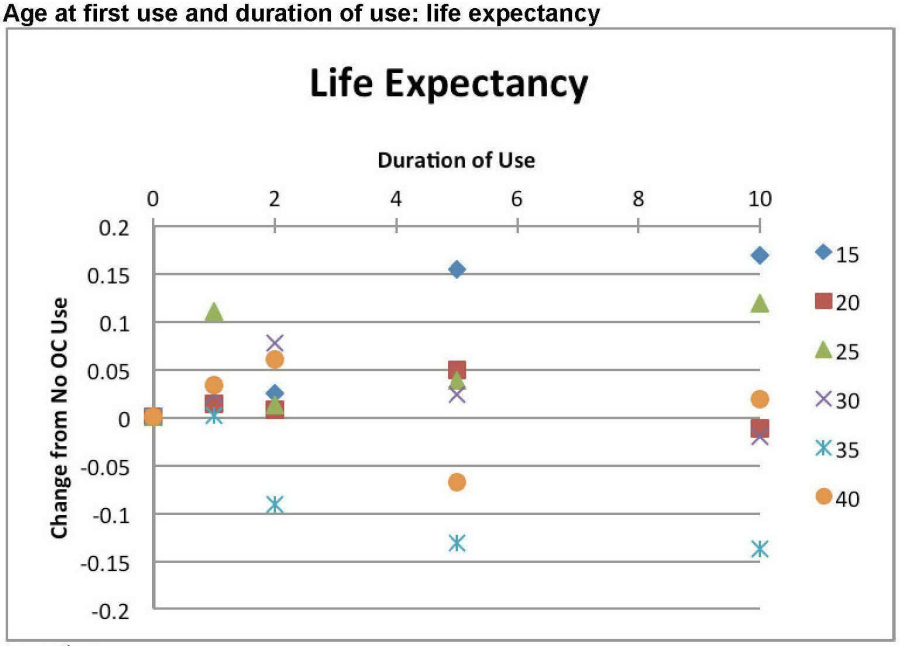
MI = myocardial infarction; OC = oral contraceptive

Figure 69. Age at first use and duration of use: myocardial infarction mortality



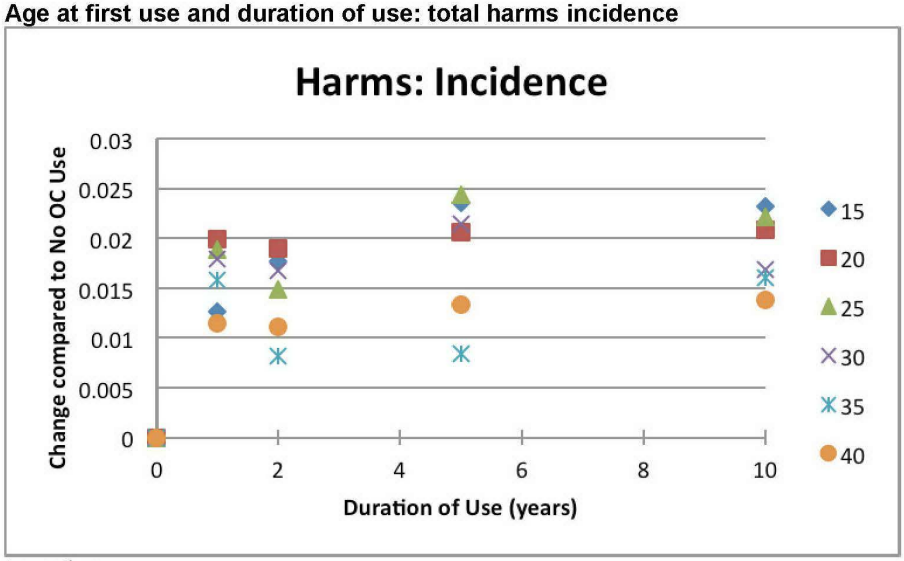
MI = myocardial infarction; OC = oral contraceptive

Figure 70. Age at first use and duration of use: life expectancy



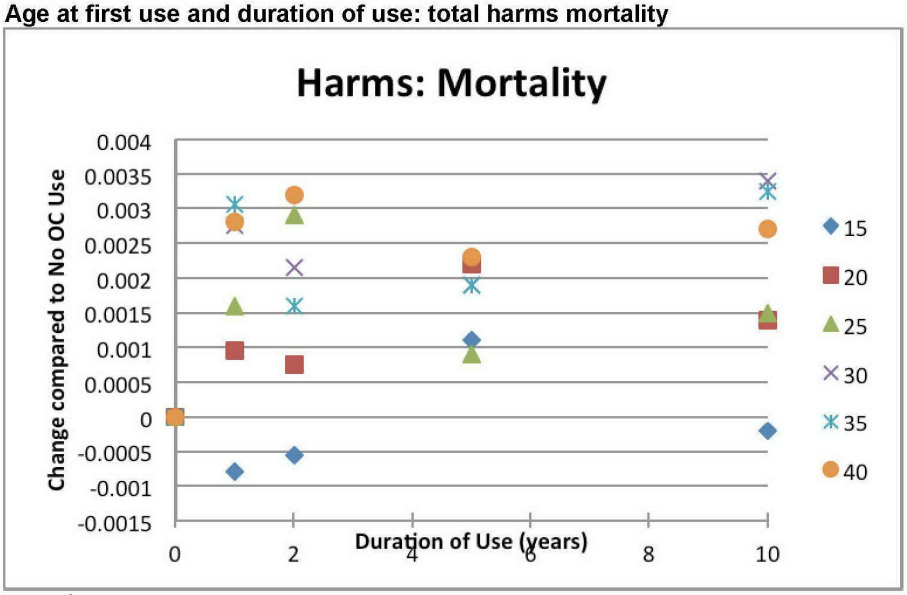
OC = oral contraceptive

Figure 71. Age at first use and duration of use: total harms incidence



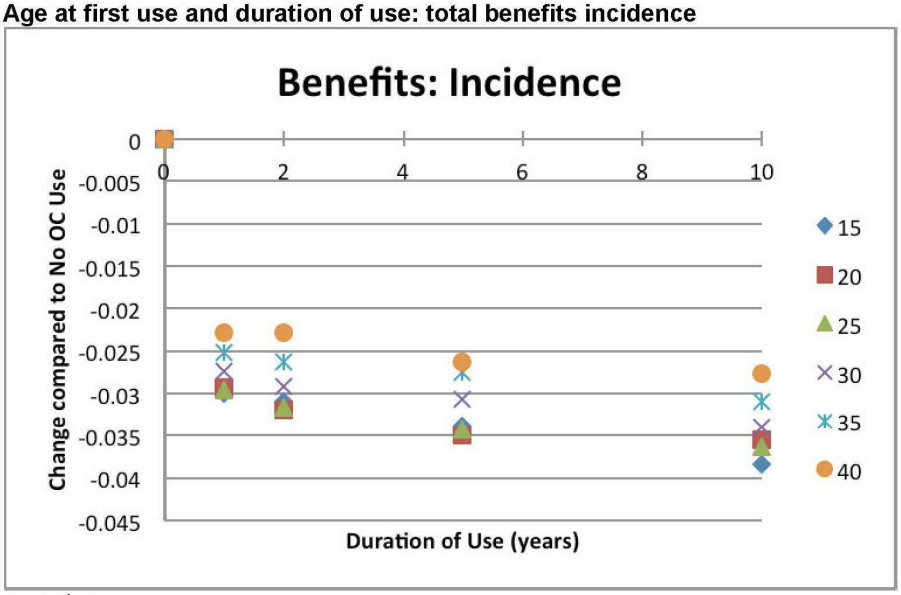
OC = oral contraceptive

Figure 72. Age at first use and duration of use: total harms mortality



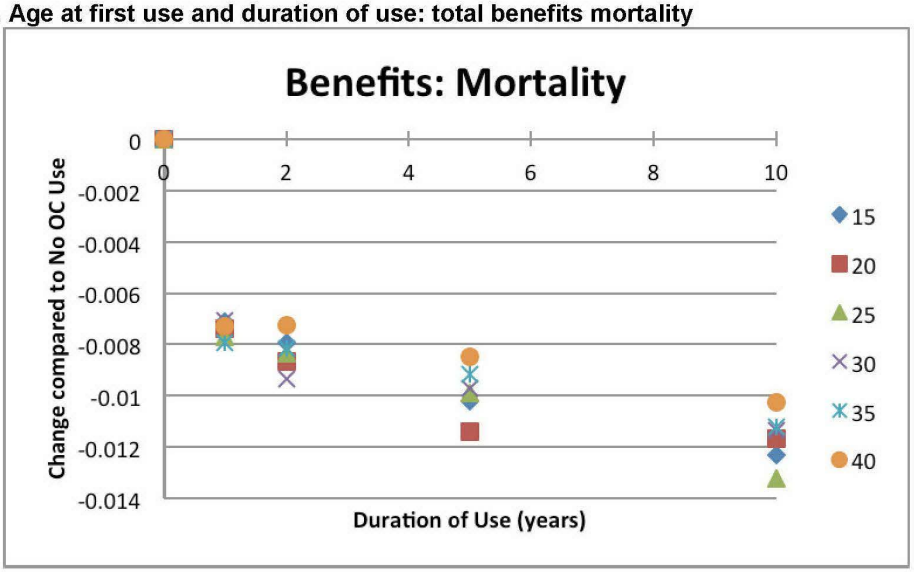
OC = oral contraceptive

Figure 73. Age at first use and duration of use: total benefits incidence



OC = oral contraceptive

Figure 74. Age at first use and duration of use: total benefits mortality



OC = oral contraceptive